Statistical Analysis Plan	
Study Code	D2500C00003
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A Phase 2 Placebo-Controlled, Randomised, Double Blind, Adaptive Dose Trial of the Safety and Efficacy of Inhaled AZD1419 in Adults With Eosinophilic, Moderate to Severe Asthma

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Study Statistician [redacted]

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Global Product Statistician [redacted] 22 Oct 2018
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Medical Science Director [redacted] 22 October 2018
Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire-5
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AZDD	Astra Zeneca Drug Dictionary
BD	Bronchodilator
BMI	Body Mass Index
CI	Confidence Interval
CompEx	Composite Endpoint for Exacerbations
CRF	Case Report Form (electronic/paper)
CSR	Clinical Study Report
CSP	Clinical Study Protocol
CV	Coefficient of Variation
DAE	Discontinuation of Investigational Product due to Adverse Event
DLco	Diffusing Capacity of the Lung for Carbon Monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ePRO	Electronic Patient Reported Outcome
FAS	Full Analysis Set
FEF 25-75	Forced Expiratory Flow at 25-75% of the forced vital capacity
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
IFN-α	Interferon
Ig, IgE, IgG	Immunoglobulin, Immunoglobulin E, Immunoglobulin G

Abbreviation or special term	Explanation
IP	Investigational Product
ITT	Intention To Treat
LABA	Long-acting Beta Agonist(s)
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed-effect Model Repeated Measures
PBMC	Peripheral Blood Mononuclear Cell
PA	CompEX diary event: Peak Expiratory Flow, Awakenings
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PEFR	Peak Expiratory Flow Rate
PGx	Pharmacogenetic
PR	CompEX diary event: Peak Expiratory Flow, Reliever use
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
PRS	CompEX diary event: Peak Expiratory Flow, Reliever use, Symptoms
PRSA	CompEX diary event: Peak Expiratory Flow, Reliever use, Symptoms, Awakenings
PS	CompEX diary event: Peak Expiratory Flow, Symptoms
PT	Preferred Term
QRS	ECG interval measured from the onset of the QRS complex to the J point
REML	Restricted Maximum Likelihood
RR	The time between corresponding points on 2 consecutive R waves on ECG
SABA	Short-Acting Beta Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Système International
SOC	System Organ Class
TBL	Total Bilirubin
VC	Vital Capacity
ULN	Upper Limit of Normal

AMENDMENT HISTORY

Date	Brief description of change
01May2018	Section 3.1.5: Added more detail regarding handling of missing data when calculating weekly means for eDiary data. Section 3.3.3: Added sentence to refer to Section 3.1.5 when calculating weekly means. Section 3.3.7: Deleted text stating that only spirometry tracings determined to be acceptable or borderline will be used. Added a sentence regarding the value of Percent predicted normal for FEV_1. Section 3.3.8: Added sentence to refer to Section 3.1.5 when calculating weekly means. Section 3.3.9: Added sentence to refer to Section 3.1.5 when calculating weekly means. Section 3.3.10: Clarified that these measurements were made pre- and post-Bronchodilator. Section 3.4.1: Added sentence regarding Flu-like Adverse Events. Section 3.4.1.1: Other Significant Adverse events section is removed. Section 3.4.3: Pulse Oximetry is replaced by Peripheral Oxygen Saturation in Table 2. Section 3.4.4: Added a sentence to refer to Table 4 for ECG reference ranges. Section 4.2.1: Identification of the five covariates to be used in Blinded Deliverable review analyses. Section 4.2.3.2: Added that compliance for FeNO will be calculated using the recordings from the NIOX Vero device at home. Changed eDiary compliance definition - replaced ‘dosing occasions’ with ‘recordings’. Section 4.2.4.2: Added k=patient subscript to mixed effect model for repeated measures analysis model definition. Section 4.2.4.3: Added k=patient subscript to mixed effect model for repeated measures analysis model definition. Section 4.2.4.4: Clarified summary statistics table. Added a sensitivity analysis summary table. Section 4.2.4.5: Added k=patient subscript to mixed effect model for repeated measures analysis model definition. Section 4.2.4.6: Added k=patient subscript to mixed effect model for repeated measures analysis model definition. Added two summary tables for PEF summary statistics (morning weekly average and evening weekly average). Section 4.2.4.12: Removed ‘Vital Capacity’ as duplicated with ‘Forced Vital Capacity’. Section 4.2.5.1: Removed Other Significant Adverse events from section as this is redundant. Added definition of Flu-like Adverse events.

Date	Brief description of change
01May2018	Section 4.2.5.5: Defined ECG reference ranges in a table. Section 5.1: Described the sensitivity analysis summary table for Reliever Medication. Section 6: Updated the section to describe further changes of analysis from protocol. Section 8.1: Updated the analysis windows of weekly summaries table. Updated the analysis windows for scheduled visits table.
14Aug2018	Section 1.3 replaced Figure 1 with the version with correct visit schedule from v3 of protocol. Section 3.1.1 Clarification of baseline definition calculations. Section 3.1.5 Removed (>50%) and no imputations of missing values. Noted to treat patients that have discontinued as a separate scenario. Included age at asthma diagnosis and years since most recent exacerbation variables in partial dates section. Section 3.4.2 Urinalysis shift-table removed. Section 3.3.1 Removed at least one and >1. Section 3.3.6 Replaced 'between the morning and evening' with 'day-time and night-time'. Section 3.3.8 Added explanation which measurements will be treated as daytime assessments and night-time assessments Section 3.3.9 Removed repeated FeNO baseline definition. Section 3.3.11 Removed (>50%). Section 3.5.1 Updated slope diary events, and added in change from baseline. Updated baseline calculation definition. Section 4.1 Removed section for log-transformed as no longer applicable. Section 4.2.1 For the final analysis, only age and gender will be included as covariates for the statistical models. Section 4.2.3 Removed 'by dose'. Section 4.2.3.2 Updated the categories for treatment compliance levels. Added clarification for treatment compliance calculation. Added clarification in FeNO, eDiary and ACQ-5 sections. Section 4.2.4.1Removed 'at least one episode' and 'since start of treatment'. Section 4.2.4.12 Replaced this section to cover how efficacy data collected during sentinel vists will be processed. Section 4.2.5.1 Updated to increase number of Flu-like AE tables. Section 4.2.5.2 Removed section 'for urinalysis' as not required. Section 4.2.5.3 Added text regarding data collected at Sentinel visits. Section 4.2.5.5 Shift table changed to be summary of change from baseline to the end of study. Section 4.2.5.7 Updated hypothesis test to be 2 sided as it is not primary. Section 5.1 Added LOCF as another imputation method required for Reliever Medication summary statistics. Included sensitivity analysis for asthma

Date	Brief description of change
	symptom scores.
	Appendix A Table 5 and 6, updated visit windows.
	Section 3.1.1 Definition of baseline added for ACQ-5.
6Sep2018	Section 3.1.4 Clarifications made regarding handing of unscheduled visits.
	Section 3.3.4 Removed paragraph describing new exacerbations as not applicable.
	Section 3.3.5 Removed '≥' as we will only capture one moderate or severe exacerbation per patient in the study.
	Study 3.4.1 Modified AE period categorisation definitions.
	Section 4.2.2 Deleted requirement for disallowed concomitant medication table
	Section 4.2.4.8 Removed 'first'as we will only only capture one moderate or severe exacerbation per patient in the study.
	Section 4.2.4.9 Removed '≥' as we will only capture one moderate or severe exacerbation per patient in the study.
	Section 6 Updated the section to describe further changes of analysis from protocol.
04Oct2018	Section 3.1.1 Added definition for mean baseline reliever medication. calculation. Added text regarding how to program if 'number of puffs of rescue inhaler' is missing.
	Section 3.3.3 Renamed 'Daily Asthma symptom scores' to 'Asthma Daily Diary'. Added worked example for Asthma Daily Diary (weekly total).
	Section 3.3.4 Removed 'first' as we will only capture one moderate or sever exacerbation per patient in the study.
	Section 3.3.6 Added clarification for how the weekly total mean reliever medication is calculated.
	Section 3.3.8 Added calculation for weekly PEF mean.
	Section 4.2.4.4 Removed the baseline term from the model.
	Section 4.2.4.5 Clarified which baseline covariate is used depending on whether pre-dose/pre-BD or pre-dose/post-BD.
	Appendix A Table 5. First column removed.
19Oct2018	Section 2.1.2 Updated FAS definition.
	Section 3.1.1 Added a definition for PEF baseline variables.
	Section 3.1.5 Clarified approach for dealing with inconsistencies in Reliever Medication responses. Added missing rule text for Asthma Daily Diary and Reliever Medication.
	Section 3.2 Made explicit that ePRO provider sets ACQ-5 to missing if responses to any questions are missing.
	Section 3.3 Removed '≥1' as we will only capture one moderate or severe exacerbation per patient in the study.
	Section 3.3.2 Made explicit that ePRO provider sets ACQ-5 to missing if responses to any questions are missing.
	Section 3.3.3 Clarified worked example for Asthma Daily Diary weekly

Date	Brief description of change
	averages. Section 3.3.4 Removed 'first' as we will only capture one moderate or sever exacerbation per patient in the study. Section 3.3.8 Clarified defintions for weekly PEF calculations. Section 3.3.11 Removed rule for setting weekly mean to missing if >4 missing daily values. Section 3.4.1 Clarification. Replaced 'occurring' with 'starting'. Section 3.4.2. Defined 'on-treatment'. Section 3.5.1 Clarified Slope Diary event calculation. Section 3.5.2 Clarified Biomarkers will not be part of CSR. Section 4.2.1 Clarification regarding Medical history and Surgical history. Section 4.2.2 Clarification on Prior and Concomitant medication definitions. Section 4.2.3.1 Specified that the dosing frequency was 7 days. Section 4.2.3.2 Clarified how to calculate the expected number of dosings/recordings. Section 4.2.4 Clarified hypothesis text and text describing model. Section 4.2.4.1 Clarified that Proc GLIMMIX will be used. Section 4.2.4.2 Results to be presented by overall and each timepoint. Section 4.2.4.3 Results to be presented by overall and each timepoint. Section 4.2.4.4 Removed covariate 'number of asthma exacerbations in the year prior to the study' from model. Section 4.2.4.5 Results to be presented by overall and each timepoint. Section 4.2.4.6 Results to be presented by overall and each timepoint. Section 4.2.4.7 Expanded MMRM section. Section 4.2.4.9 Clarified text describing model. Section 4.2.5.2 Defined 'on-treatment'. Section 5.1 Clarified that Proc GLIMMIX will be used. Section 6 Described update to FAS definition.

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D2500C00003. The SAP describes the statistical analyses specified in the clinical study protocol (CSP) in more detail; any changes with regards to what is already specified in the CSP will be described in Section 6.

This statistical analysis plan (SAP) is based on version 3.0 of the clinical study protocol (CSP – 17 October 2016) for the study D2500C00003.

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	**Outcome Measure:**
To assess the efficacy of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment Inhaled Corticosteroids (ICS) + Long-acting Beta Agonist(s) (LABA)	Time to loss of asthma control. Loss of asthma control is defined by any of the following: • An increase of Asthma Control Questionnaire (ACQ-5) to 1.5 or more • A reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days • At least six additional relieve inhalations of Short-Acting Beta Agonists (SABA) in a 24-hour period relative to baseline on 2 consecutive days • An exacerbation requiring systemic corticosteroids

1.1.2 Secondary Objectives

Secondary Objective:	Outcome Measure:
To further assess the efficacy of inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	• Proportion of patients who experience loss of asthma control. • Changes over the course of the study in ACQ-5. • Changes over the course of the study in asthma daily diary score. • Changes over the course of the study in number of moderate and severe exacerbations. • Changes over the course of the study in the use of reliever bronchodilator (short-acting beta-agonist SABA). • Changes over the course of the study in pre- and post-bronchodilator Forced Expiratory Volume in 1 second (FEV_1). • Changes over the course of the study in Peak Expiratory Flow (PEF). • Changes over the course of the study in Fractional exhaled nitric oxide (FeNO)

1.1.3 Safety objective

Safety Objective:	Outcome Measure:
To evaluate the safety and tolerability of AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	• Adverse events, vital signs, electrocardiogram (ECG), and laboratory parameters • Weekly peak expiratory flow rate (PEFR) • Lung diffusion capacity (DLco)

1.1.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
• To assess the responses of selected systemic peripheral blood and sputum biomarkers to inhaled AZD1419 in eosinophilic asthma patients after withdrawal of controller treatment of ICS + LABA	• Peripheral blood and sputum biomarkers • Other biomarkers may be considered
• To assess the composite endpoint for exacerbations, CompEx	• Time to first CompEx event • Changes over the course of the study in number of CompEx events
• To investigate the genes and genetic variation that may influence response to AZD1419	• DNA from whole blood
• To assess the expression of selected genes in cells from the whole blood and sputum	• RNA from whole blood and sputum
• To assess the effects on DNA methylation	• DNA from whole blood
• To assess the immune function of PBMC	• PBMCs

Results from the exploratory analyses, if performed, may be reported separately from the Clinical Study Report (CSR).

The analysis of all exploratory variables other than CompEx will be outside the scope of this SAP.

1.2 Study design

This is a randomised, double blind, placebo-controlled Phase 2a study designed to assess the efficacy and safety of 13 once weekly doses of inhaled AZD1419 administered to patients with eosinophilic asthma controlled on a maintenance treatment of Inhaled Corticosteroids (ICS) plus a Long-acting Beta Agonist(s) LABA but no other controller medication.

This study is a multi-centre study conducted at 16 centres in 4 countries.

Prior to randomisation patients will undergo an approximately 2-4 weeks screening period. Eligible patients will be prescribed their usual controller medication (i.e. ICS + LABA in separate inhalers, in addition to a rescue medication inhaler (short-acting B2 agonist [SABA]), and issued electronic diaries, peak flow and FeNO meters to record asthma symptoms and lung function during each morning and evening at home. Asthma control will be assessed using the 5-item asthma control (ACQ-5) and when patients have shown to be controlled (ACQ-5<= 0.75) they are randomised to receive AZD1419 or placebo administered as an inhalation at the clinic once per week.

A withdrawal design will be used where the first 6 doses of investigational product (IP) will be administered as add-on to the patient's regular ICS + LABA medication. The controller

medication will then be tapered down and discontinued during the next 3 doses of IP, and the last 4 doses will be administered during a period of complete ICS and LABA withdrawal (see Figure 1). In addition the study drug dose level will be adjusted using an adaptive dosing scheme (defined in Section 4.2.2 of the protocol) based on appearance of flu-like symptoms. The primary endpoint is loss of asthma control, defined in Section 1.1.1. When a patient meets the primary endpoint, the patient will resume ICS + LABA and will be followed for an additional 4 weeks before discontinuing the study.

The total duration of patient participation will be up to 56 weeks. Prior to randomisation patients will undergo an approximately 2-4 week screening period, which is then followed by a 12 week dosing period and an up to 40 week observation period following the last dose. The study design is presented in Figure 1. The schedule of trial procedures is presented in Table 1 of the CSP.

The study will start with a sentinel dosing period to be conducted at 1 or 2 selected study centres during which 4 patients will be randomly assigned 1:1 either to placebo or AZD1419 at 4 mg, dosed once weekly. Sentinel patients will be observed at the clinic for 24 hours after each of the first two doses, for details see Section 4.2.1 of the protocol. A Data Safety Monitoring Board (DSMB) will review safety data from these patients and approve enrolment of additional patients into the study.

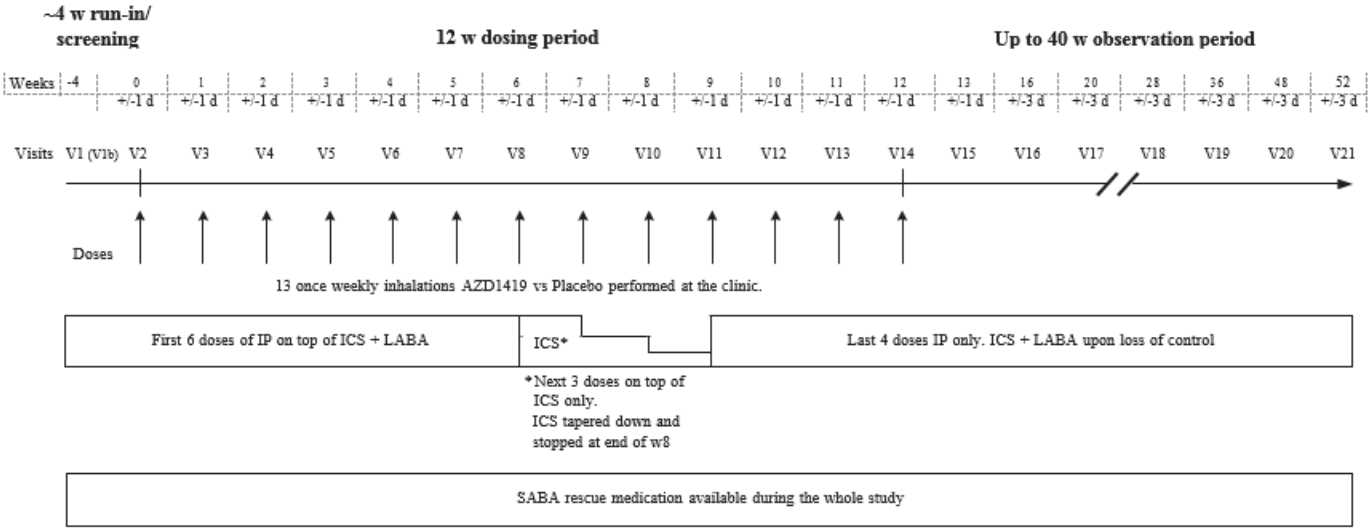
Patients will be monitored with regards to safety, tolerability and efficacy aspects during the whole study period. In addition to assessments performed at the clinical visits, an electronic patient reported outcome (ePRO) device coupled with a home spirometer will on a daily basis capture asthma symptoms, relieve use, lung function peak expiratory flow (PEF) and a fractional exhaled nitric oxide (FeNO) meter measurements will be performed every second day.

1.3 Number of patients

This trial has about 90% power to yield a statistically significant (alpha = 0.05, 2-sided) difference between the pooled active and placebo groups in time to loss of asthma control given that the cumulative number of controlled patients at week 52 is 20% and 60% for control versus active respectively. Assuming a drop-out of about 10-15%, this will require about 70 patients in total (32 events).

Approximately 135 patients have been enrolled to achieve 81 randomised patients.

Figure 1 Study flow chart



2. ANALYSIS SETS

2.1 Definition of analysis sets

All efficacy analyses will be performed using an intention-to-treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analysed based on the Safety population.

Table 1 Summary of Outcome Variables and Analysis Populations

Objective	Outcome Variable	Population
Efficacy	Time to Loss of Asthma Control	FAS
	Proportion of patients experience loss of asthma control	
	ACQ-5	
	Asthma daily diary score	
	Moderate or severe exacerbations	
	Proportion of subjects with ≥ 1 moderate or severe exacerbation during 52 weeks of treatment	
	Reliever medication use	
	FEV1	
	PEF	
	FeNO	
	FVC and FEF 25-75%	
	Night-time awakenings	
Safety	AEs	SA
	Vital Signs	
	ECG	
	Laboratory parameters	
	DLco	
Exploratory	CompEx	FAS

2.1.1 All patients analysis set (All Patients)

This analysis set will comprise all patients screened for the study and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set (FAS)

All patients with a signed ICF who were randomised and receiving any IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment, irrespective of whether or not they received the wrong IP, and irrespective of whether they prematurely discontinued the study. For patients who withdraw consent to participate in the study all data will be included up to the date of their study termination.

2.1.3 Safety analysis set

All patients who received any IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has one, or several occasions, received active treatment will be classified as active. Patients will be classified according to the following:

- If a patient receives at least one dose of AZD1419 they will be included in the active treatment group.
- If a patient receives placebo only, they will be included in the placebo treatment group.

All safety summaries will be based on this analysis set. Any deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data.

2.2 Violations and deviations

Only important protocol deviations will be listed and tabulated in the CSR. Protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being include:

- Patients who do not meet the inclusion criteria
- Patients who do not meet the randomisation criteria
- Patients who meet any of the exclusion criteria
- Patients who use one or more disallowed medication (for any reason, unless otherwise specified) during the randomised treatment period. A list of concomitant medications for all subjects will be provided for physician review before each data review meeting, for the identification of disallowed medication.

- Patients who received the incorrect study treatment or study dose at any time during the 12-week double blind treatment period
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients who do not take ICS + LABA regime as per the study schedule

All-important protocol deviations will be identified and documented prior to unblinding of the data.

Important deviations will be programmatically derived. In addition, an IMPACT report will be provided by the AZ Study lead in an Excel file. The IMPACT report will be reviewed together by the study team in order to make decisions regarding patient evaluability. The protocol deviation classification process and data flow will be clarified in a separate document.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General Principles

3.1.1 Baseline definitions

In general, the last measurement on or prior to the date of randomisation will serve as the baseline measurement for efficacy endpoints, while the last measurement prior to first dose of IP will serve as the baseline measurement for safety endpoints.

For the following parameters, only measurements recorded at the baseline visit (Visit 2 (Week 0)) taken pre-bronchodilator are considered for the baseline: Inspiratory Capacity (IC), FEV_1/FVC ratio, FEV_1 reversibility, FEV_1 reversibility (%), Diffusing Capacity of the Lung Carbon Monoxide (DLco), FeNO, average FeNO.

If Visit 2 (Week 0) measurement is missing, the last non-missing value before Visit 2 will be used as baseline instead.

For the following parameters, baseline is calculated at each timepoint (pre-bronchodilator and post-bronchodilator): FEV_1, Forced Vital Capacity (FVC), Forced Expiratory Flow 25%, Forced Expiratory Flow 75%, Forced Expiratory Flow 25% to 75% (FEF25-75%) and PEF (collected at the clinic). For post-bronchodilator (BD) measurements, where it is possible to have multiple spirometry records per time point, the first measurement will be used (i.e. the measurement after the first BD administration).

The baseline for Electronic Patient Reported Outcome（ePRO) will be derived from what is captured on the ePRO device 5 days prior to Visit 2 (Week 0) for PEF, Asthma Daily Diary scores and Reliever medication use. The 5 days do not have to be strictly consecutive.

For night-time baseline diary scores, the calculations should comprise 5 mornings including the morning of randomisation. For daytime baseline diary scores, the calculations should comprise 5 evenings prior to randomisation.

For PEF evening baseline mean, the calculations should comprise of the mean of last 5 evening values prior to randomisation. For PEF morning baseline mean, the calculations should comprise of the mean of last 5 morning values prior to and including day of randomisation. For PEF baseline mean, this is calculated as the average of the morning baseline mean and the evening baseline mean.
The mean baseline usage of reliever medication will be calculated as the sum of puffs of reliever medication (last 5 morning usages + last 5 evening usages prior to visit 2 (randomisation))/5. The morning session at visit 2 is included in the calculation. If in the reliever medication diary data ASMDMQ2=0 (i.e. Use of rescue medication is response to symptoms=No) and ASMDMQ2A=missing (Number of puffs of rescue inhaler=missing), then EXDOSE will be set to zero in the SDTM datasets.

The baseline for ACQ-5 will be captured at the baseline visit (Visit 2 (Week 0)). If more than one result is captured prior to the date of randomisation, then the result from the closest prior visit will be used.

The baseline at clinic FeNO measurements will be captured at clinic at the baseline visit (Visit 2 (Week 0)). As the first FeNO measurement taken at home on the Niox Vero FeNO device will be captured at Visit 2+2d (Week 0 +2d), i.e. 2 days post first administration of IP, the clinic FeNO measurement taken at baseline visit will be the baseline for this endpoint.

For demography, laboratory data, vital signs, physical examination and ECG, baseline will be defined as the latest non-missing assessment prior to first dose at the baseline visit (Visit 2 (Week 0)). If no time is recorded for an assessment, and the assessment takes place at Visit 2 (Week 0), this will be assumed to be a pre-dose assessment.

3.1.2 Study day

Whenever data is summarised over time, study day will be calculated based on the actual assessment date. Efficacy data assessments will be summarised in relation to date of randomisation. Safety data will be summarised in relation to date of first dose.

If actual assessment date is prior to randomisation / first dose then study day will be:

Study day = Actual assessment date – Randomisation / first dose date.

If actual assessment date is on or after randomisation / first dose then study day will be:

Study day = Actual assessment date – Randomisation / first dose date + 1.

3.1.3 Absolute and percent change from baseline

Absolute change from baseline outcome variables is computed as

(post-randomisation value – baseline value).

Percent change from baseline is computed as

((post-randomisation value – baseline value) / baseline value) × 100%.

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

Percentage change from baseline will not be calculated or presented for variables that may take 0 as a value.

3.1.4 Visit windows

For the exacerbation-related analyses no windows will be applied.

Daily eDiary and ePRO data (PEF, ACQ-5, FeNO) will primarily be summarised and analysed as weekly averages e.g. over days 2 - 8, 9 - 15 and 16 - 22 etc, separately. The assessment period of visit windows will be defined in Appendix A, Table 5.

Summaries and analyses of non-eDiary or non-ePRO data will be based on CRF visit designation, defined in Appendix A, Table 6.

Any data collected at unscheduled visits will be listed, included within baseline data in shift plots, and will be included in the definition of maximum/minimum within-period value.

The Unscheduled visits will be included when applying the visit windows to ensure that all available data are used in the analysis. For weekly summaries, the mean of all non-missing observations within an assigned window is calculated. For visit data, if there are duplicate observations assigned to the same visit window, the following data handling conventions will be adopted:

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

2. If two observations are collected on the same day, the non-missing observation with the later collection time will be included in the analysis.

3.1.5 Handling of missing data

All efficacy analyses will be based on the Full Analysis Set. Missing data rules for efficacy endpoints can be found in Sections 3.2 and 3.3. For eDiary endpoints (derived datasets ADQS, ADRE, ADEXSUM), when weekly means are calculated for summary statistics this will be calculated as the average of the non-missing values over a period of 7 sequential days e.g. if non-missing values are only recorded for 3 days then the denominator for the mean is 3. For

rescue medication weekly mean calculation where a patient discontinues treatment part-way through a week, the mean would be calculated as the average of what is recorded regardless of how many days were recorded in that part-week. For the eDiary endpoint rescue medication, in the event that a patient has recorded that they have taken rescue medication (ASMDMQ2=1) but the associated number of puffs collected is missing or recorded as zero (ASMDMQ2A=missing or 0), this missing or zero value will be changed to EXDOSE=1 in the SDTM datasets,

As the daily total for Asthma Daily Diary scores and Reliever medication are defined as the sum of the daytime and night-time scores on a specific day (e.g. sum of day 1 evening plus day 2 morning), if either daytime or night-time scores is missing, the daily total is set to missing.

Missing safety data will not be imputed.

Laboratory values of the form "<x" (i.e. below the lower limit of quantification) or ">x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.

For the diagnosis of Allergic Rhinitis, age at asthma diagnosis, years since most recent exacerbation and similar variables based on date calculations, if only partial dates are recorded, these will be imputed as the earliest possible date e.g. if day is missing but month and year are present then the 1st of the month will be imputed in order to derive the time since diagnosis variable. If the day and month are missing but the year is present, then the 1st January of that year will be imputed in order to derive the time since diagnosis variable. Partial dates will be flagged in listings and the analysis.

3.2 Primary efficacy outcome measure

The primary outcome measure is time to loss of asthma control. The EXACA module of the eCRF will be used to derive the Loss of asthma control variable. For the purpose of the study, loss of asthma control is defined as any of the following:

a) An increase of ACQ-5 to 1.5 or more

   In the ACQ-5 questionnaire the patients are asked to recall the status of their asthma during the previous week with regards to symptoms. The questionnaire include questions on

   1. Awoken at night by symptoms
   2. Limitation of normal daily activities
   3. Waking in the morning with symptoms
   4. Dyspnoea
   5. Wheeze

The questions of the ACQ-5 will be measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-5 score is computed as the un-weighted mean of the responses. If response to any of the questions is missing, the ACQ-5 score is set to missing by the ePRO provider. If ACQ-5 reaches a value of 1.5 or more, the patient is reported as having loss of asthma control.

b) A reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days

   PEF is measured daily using the ePRO device. Patients should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing; the highest of the 3 values will be captured for the morning and for the evening manoeuvres.

c) At least six additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days

   The number of reliever medication inhalations taken will be recorded by the patient in the Asthma Daily Diary twice daily. The number taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning. Reliever medication usage is captured in the daily diary as the number of inhaler puffs.

d) An exacerbation requiring systemic corticosteroids

Upon a), b) or c) being fulfilled, an automated asthma action plan will be triggered in the ePRO device prompting the patient to resume their usual ICS + LABA medication and to contact the PI.

The primary endpoint Time to loss of asthma control will be calculated as follows:

Start Date of first loss of asthma control – Date of Randomisation + 1.

The start date of the first loss of asthma control will be the earliest of:

1. Date of the first increase in ACQ-5 of 1.5 or more
2. Date of the first of two consecutive days with a reduction of 30% or more in PEF
3. Date of the first of two consecutive days with six additional SABA inhalations relative to baseline
4. Date of the earliest use of systemic corticosteroids to treat an asthma exacerbation

Time to loss of asthma control will be censored at 52 weeks for patients who do not experience loss of asthma control during the 52-week study period or at the time point after which an loss of asthma control experience could not be assessed (for lost-to-follow-up patients). For patients who withdraw from the study without reporting loss of asthma control, time will be censored at the date of withdrawal, if known, else at the patient's last clinical visit plus one day.

3.3 Secondary endpoints

Secondary efficacy variables include proportion of patients with loss of asthma control, ACQ-5, eDiary variables, proportion of patients with a moderate or severe exacerbation, PEF, FEV_1 and FeNO. These are described in more detail below.

3.3.1 Proportion of patients who experience loss of asthma control

The proportion of patients who experience loss of asthma control during the 52-weeks of treatment will be a supportive measurement to the primary objective. The outcome variable will categorize each patient as having loss of asthma control symptom being met or not (yes=1/no=0).

The proportion of such patients will be calculated for each treatment group as:

Number of patients with loss of asthma control indication during the 52-week treatment period/ number of patients in treatment group

3.3.2 Asthma Control Questionnaire (ACQ-5)

In the ACQ-5 questionnaire the patients are asked to recall the status of their asthma during the previous week with regards to symptoms, see Section 3.2 for specific questions.

The ACQ-5 questions will be measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-5 score is computed as the un-weighted mean of the responses. If response to any of the questions is missing, the ACQ-5 score will be set to missing by the ePRO provider. If ACQ-5 reaches a value of 1.5 or more, the patient is reported as having loss of asthma control.

As mentioned above, the ACQ is based on 5-item version. The ACQ-5 will be self-administered within the ePRO once weekly during the study.

The outcome variable for ACQ-5 is a weekly average.

3.3.3 Asthma daily diary score

Asthma symptoms during night-time and daytime will be recorded by the patient each morning and evening in the Asthma Daily Diary. Symptoms will be recorded using a scale 0-3, where 0 indicates no asthma symptoms. The outcome variables, asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning), and total score will be calculated and presented separately.

The outcome variable Asthma Daily Diary total score will be calculated by taking the sum of the night-time and daytime asthma symptom scores recorded each day. The outcome variable Asthma Daily Diary total weekly mean for a specific week will be calculated as the sum of non-missing daily total is divided by the number of non-missing days of that week. If a patient is missing a value for either night-time or daytime asthma symptom score on a given day, then the total score for that day will be set to missing.

Example for Asthma Daily Diary total weekly mean calculation:

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Morning	Prior randomisation night-time scores (D1_M)	Day 1 night-time scores (D2_M)	Day 2 night-time scores (D3_M)	Day 3 night-time scores (D4_M)	Day 4 night-time scores (D5_M)	Day 5 night-time scores (D6_M)	Day 6 night-time scores (D7_M)	Day 7 night-time scores (D8_M)
Evening	Daytime scores on Day 1 (D1_E)	Day 2 daytime scores (D2_E)	Day 3 daytime scores (D3_E)	Day 4 daytime scores (D4_E)	Day 5 daytime scores (D5_E)	Day 6 daytime scores (D6_E)	Day 7 daytime scores (D7_E)	Day 8 daytime scores (D8_E)

Total daily scores for each day is defined as: D(n)_E+D(n+1)_M, where n = 1, 2, ..7

Week 1 morning mean, W1_M,: (D2_M+..+D8_M)/7. "/7" is for illustration in this example, the number of non-missing days will be used in the analysis.

Week 1 evening mean, W1_E, is defined as: (D1_E+…+D7_E)/7. "/7" is for illustration in this example, the number of non-missing days will be used in the analysis.

Total daily scores on a weekly basis should be [D(n)_E+D(n+1)_M]/7 where n=1,…7. "/7" is for illustration in this example. The number of non-missing number of days will be used in the analysis.

The number of asthma symptom-free days will be calculated for each patient as the total number of days in the 52 week treatment period where the total asthma symptom score is 0. The outcome variable proportion of asthma symptom-free days will be calculated using the total number of days with completed asthma symptom score diary during the 52-week treatment period as the denominator.

Summary statistics will be presented by treatment and week for the number of asthma symptom-free days and the proportion of asthma symptom-free days. The handling of missing data in the calculation of weekly average daytime asthma daily diary score, weekly average night-time asthma daily diary score and weekly average total asthma daily diary score is described in Section 3.1.5.

3.3.4 Time to moderate or severe exacerbation

Severe exacerbation is defined as a worsening in asthma symptoms and

- Use of systemic corticosteroids for at least three days and/or
- An unscheduled visit or emergency room visit due to asthma symptoms that requires at least one dose of systemic corticosteroids and/or

- An in-patient hospitalization due to asthma requiring at least one dose of systemic corticosteroids.

Moderate exacerbation is defined as a temporary increase in maintenance therapy in order to prevent a severe event supported by a sustained (≥ 2 day) worsening in at least one key control metric i.e. asthma score, reliever medication use, night time awakening or morning PEF.

The start and stop dates of severe exacerbations experienced by a patient during the treatment period will be derived from the following rule.

- The start date of a severe exacerbation is defined as the start date of systemic corticosteroids or increased use of systemic corticosteroids or of emergency room visit or hospital admission, whichever occurs first.

- The stop date is defined as the last day of systemic corticosteroids/increased use of systemic corticosteroids or hospital discharge, whichever occurs last.

The start and stop dates of moderate exacerbations experienced by a patient during the treatment period will be derived from the following rule.

- The start date of a moderate exacerbation is defined as the first day of increase in temporary maintenance therapy.

- The stop date is defined as the last day of this treatment.

The EXACA module of the eCRF will be used to derive the severe exacerbation variable. The MED1 module of the eCRF will be used to derive the moderate exacerbation variable.

Time to a moderate or severe exacerbation will be censored at 52-weeks for patients who do not experience a moderate or severe exacerbation during the 52-week study period or at the time point after which a moderate or severe exacerbation experience could not be assessed (for lost-to-follow-up patients). For patients who withdraw from the study without reporting a moderate or severe exacerbation, time will be censored at the date of withdrawal, if known, else at the patient's last clinical visit plus one day.

As defined for the primary analysis, exacerbations that occur after a subject has discontinued IP but before maximum follow-up time will still be accounted when deriving the total number of exacerbations. Likewise, the follow-up time will reflect the follow-up time regardless of whether or not the subject is still on IP.

3.3.5 Proportion of subjects with 1 moderate or severe exacerbation during 52-weeks of treatment

The proportion of patients who experience 1 moderate or severe exacerbation during the 52-weeks of treatment will be a supportive measurement to the primary objective. The outcome variable will categorize each patient as having one moderate or severe exacerbation experience being met or not (yes=1/no=0).

The proportion of such patients will be calculated for each treatment group as:

Number of patients with 1 moderate or severe exacerbation during the 52-week treatment period/ number of patients in treatment group

3.3.6 Reliever medication use

The number of rescue medication inhalations taken will be recorded by the patient in the Asthma Daily Diary twice daily. The number taken at daytime lung function assessments will be recorded in the evening. The number of inhalations taken at night-time lung function assessments will be recorded in the morning. Reliever medication usage is captured in the daily diary as the number of inhaler puffs.

The number of inhalations (puffs) per day will be calculated as follows:

Number of night inhaler puffs + number of day inhaler puffs

The outcome variable total weekly mean reliever medication use for a specific week will be calculated the same way as total weekly Asthma Daily Diary scores in Section 3.3.3, i.e. Day 1 should be D1_E+D2_M, and the weekly mean is (D1 total +D2 total+..+D7 total)/ non-missing number of days.

3.3.7 FEV_1 pre/post BD

The pre/post BD FEV_1 will be determined by the spirometry tests at the clinic at each visit as scheduled. To ensure quality control all spirometry measurements are reviewed to ensure that they meet ATS/ERS (American Thoracic Society 2000) criteria for acceptability. Section 5.1.2 of the CSP contains further details of the spirometry recordings.

The endpoints are:

1) absolute change from baseline in pre-BD FEV_1 (L)
2) percentage change from baseline in pre-BD FEV_1
3) absolute change from baseline in post-BD FEV_1 (L)
4) percentage change from baseline in post-BD FEV_1

The absolute changes from baseline are the main FEV_1 endpoints. The percentage changes from baseline are supportive endpoints.

A reversibility test will be performed at Visit 1 (Week -4), with spirometry assessment 30±10 minutes before and after administration of short-acting β2 agonist.

The percent reversibility is calculated as follows:

Reversibility (%) = (FEV_1 post – FEV_1 pre) / FEV_1 pre x 100

The value of Percent predicted normal for FEV_1 used as part of the eligibility process will not be checked programmatically.

3.3.8 Peak Expiratory Flow (PEF)

Morning and evening PEF measurements will be taken at home on the ePRO device by the patient on a daily basis and then averaged over the week. The outcome variable is weekly average total PEF. The weekly morning PEF average for Week 1 is calculated as (D2_M+..+D8_M)/non-missing days) and weekly evening PEF average is calculated as (D1_E+…+D7_E)/non-missing days). Weekly average total PEF is calculated as the average of the weekly morning mean and the weekly evening mean. The handling of missing data is described in Section 3.1.5.

3.3.9 Fractional Exhaled Nitric Oxide (FeNO)

FeNO measurements will be taken at home by patients every second day. FeNO measurements will also be taken at designated time points at the study centre.

The home FeNO outcome variable is a weekly average FeNO based on the average of measurements taken at home for a specific week. The handling of missing data in the calculation of weekly average FeNO is described in Section 3.1.5.

The home FeNO outcome variable will be separate to the clinic FeNO outcome variable.

3.3.10 Vital Capacity and Forced Expiratory Flow at 25-75%

FVC and FEF25-75 are spirometry measurements taken pre- and post- BD at clinic visits 1 (Week -4), 2 (Week 0), 6 (Week 4), 9 (Week 7), 14 (Week 12), 15 (Week 13), 16 (Week 16), 17 (Week 20), 18 (Week 28), 19 (Week 36) and 21 (Week 52).

Summary statistics will also be presented for each treatment group at the specified visits.

3.3.11 Night time awakenings

Night-time awakenings due to asthma symptoms will be recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response.

Summary statistics will also be presented for each treatment group at each week.

The outcome variable is a weekly mean calculated as the number of times the subject answered ‘yes’ over a period of 7 sequential days. The first weekly mean (the treatment weekly mean) will be based on the morning recording on Day 2 up to and including the morning recording on Day 8. The second weekly mean (the follow-up weekly mean) will be based on the morning recording on Day 9 up to and including the morning recording on Day 15 and so on.

3.4 Calculation or derivation of safety variable(s)

The following safety data will be collected: vital signs, physical examination (include 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, 12-lead ECG, haematology, clinical chemistry, urinalysis, DLco, PEFR and reported adverse events (AEs).

Change from baseline (Visit 2) to each post-baseline time point where scheduled assessments were made will be calculated for relevant measurements.

3.4.1 Adverse events

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given in Sections 6.1 and 6.2 of the CSP.

All AEs recorded in the eCRF will be coded according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

All adverse events will be listed for each patient and summarised by treatment actually received. Treatment-emergent AEs will be tabulated (number and percentage of patients) by system organ class (SOC), preferred term (PT), intensity and relation to study medication.

Any AE occurring before the start of study treatment will be included in the data listings but will not be included in the summary tables of AEs and excluded from safety analysis set.

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

AE data will be categorized according to their onset date into the following periods:

- AEs starting during pre-treatment (onset date ≥ Visit 1 (Week -4) and before the first dose of IP)
- AEs starting during study (onset date ≥ the first day of IP and ≤ Visit 21 (Week 52))
- AEs starting during ICS + LABA treatment period (onset date ≥ the first day of IP and < Visit8 (Week 6))
- AEs starting during ICS taper down period (onset date ≥ Visit 8 (Week 6) and < Visit 11 (Week 9))
- AEs starting during remainder of study (onset date ≥ Visit 11 (Week 9) ≤ Visit 21 (Week 52))

The timing of AEs will be assigned to the period in which they first started. The same during treatment definition will be used for laboratory and physical examination data, where applicable. Note, not all Exacerbations will be recorded as AEs.

Common AEs, AEs with outcome of death, SAE, DAEs and Flu-like AEs will be summarized separately. Flu-like AEs are defined in Section 4.2.5.1.

3.4.2 Laboratory

Blood and urine samples will be used for determination of clinical chemistry, haematology and urinalysis parameters taken at scheduled time points as specified in Table 1, Section 4 of the CSP. The laboratory parameters to be measured are given in Table 3, Section 5.2.1 of the CSP. Laboratory data will be reported using Système International (SI) units.

Changes in haematology and clinical chemistry variables between baseline and each subsequent scheduled assessment will be calculated.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory or local laboratory (for assessments measured at a local laboratory) reference ranges will be used for laboratory variables. All values (absolute and change) falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), trace, or positive (+) at each time-point and will be listed only.

For the purposes of haematology and clinical chemistry shift tables, baseline will be defined as the latest non-missing assessment prior to first dose, and during-study is as defined in Section 3.4.1. Shift-tables will not be presented for the specific periods separately, i.e. ICS+LABA treatment period, ICS taper-down period or during the remainder of study. On treatment is defined as from date of first dose and including visit 14 (week 12).

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

$$\text{Multiple} = \text{Value} / \text{ULN}$$

i.e. if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

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

- AST $\geq$ 3xULN
- ALT $\geq$ 3xULN
- TBL $\geq$ 2xUL

3.4.3 Vital signs

Vital sign assessments (pulse, systolic blood pressure, diastolic blood pressure and pulse oximetry), will be performed as in accordance with the schedule provided in Table 2, Section 4 in the CSP. Height and weight will be assessed at screening only.

Change from baseline in vital signs will be calculated for each post-randomisation visit.

Absolute values for vital signs will be compared to the relevant reference ranges and classified as low (below range), normal (within range or on limits of range) and high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Body mass index will be calculated from the height (in meters) and weight (in kilograms) as follows:

$$BMI = kg/m^2$$

Table 2 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change Criteria
Diastolic Blood Pressure*	mmHg	<60	>100	±15
Systolic Blood Pressure*	mmHg	<90	>160	±30
Pulse*	Beats/min	<50	>100	±20
Peripheral Oxygen Saturation	%	<90	=100	N/A

* Will be taken lying down

3.4.4 Electrocardiograms (ECG)

Twelve-lead ECG measurements will be recorded in accordance with the protocol at screening and at the safety follow-up visit at the end of the trial.

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

Abnormal values shall not be recorded as AEs unless deemed clinically significant. The printout of the ECG is to be signed, dated and filed in the Investigator study file along with a signed and dated copy (if the printouts are not on archive-quality paper).

The reference ranges for the ECG tests are presented in Table 4.

3.4.5 Physical examination (not stated in the safety outcome measures)

Complete physical examinations will be performed at Visits 1 (Week -4), 6 (Week 4), 9 (Week 7), 15 (Week 13) and 21 (Week 52). Any new or aggravated existing finding(s) judged as clinically significant by the Investigator, at any post baseline physical examination during the study, compared to the screening (i.e. Visit 1) assessment will be reported as an AE.

3.4.6 Diffusing Capacity of the Lung for Carbon Monoxide

Measurement of the diffusing capacity of the lung for carbon monoxide (DLco) will be performed at Visits 1 (Week -4), 2 (Week 0), 6 (Week 4), 9 (Week 7), 15 (Week 13) and 17 (Week 20).

3.5 Calculation or derivation of exploratory endpoints

3.5.1 Composite endpoint for exacerbations (CompEx)

CompEx (Anne L Fuhlbrigge et al. 2017) will be assessed in two ways: (i) as time to first CompEx event during the 52-weeks following randomisation and (ii) as proportion of patients with a CompEx event during the 52-weeks following randomisation.

A CompEx event is defined as the first occurrence of either a diary event or a severe exacerbation.

For the development of CompEx, the following diary variables are particular of interests: peak expiratory flow (P), reliever medication use (R), asthma symptoms (S) and night-time awakening (A). Diary events for the purpose of this study, which must include peak expiratory flow (P), are defined as either at least two variables fulfilling threshold criteria, or at least one variable fulfilling a threshold criterion and the slopes for all variables fulfilling the slope criteria.

Deterioration criteria for the individual diary event are defined as either changes from baseline, larger than a pre-specified threshold for at least 2 consecutive days, or as a worsening greater than a certain magnitude (slope) over at least 5 days.

The baseline levels of deterioration should be calculated for each individual as the mean over the 5 days ending just before the day of randomisation for each of the diary variables (they do not have to be 5 consecutive days). If <5 days data are available, then take the mean for the number of days where data is collected, and if missing, the first 3 days after randomisation should be used. No imputation of missing diary data after randomisation should be performed.

Five variants of CompEx (based on diary records Peak expiratory flow and Reliever medication use (PR); Peak expiratory flow and Symptoms (PS); Peak expiratory flow and Awakenings (PA); Peak expiratory flow, Reliever medication use and Symptoms (PRS) and Peak expiratory flow, Reliever mediation use, Symptoms and Awakenings (PRSA) respectively) will be explored and are defined in Table 3 along with criteria for events in term of thresholds and slopes. PRS is pre-specified to be the primary diary event endpoint of interest.

A diary event required the fulfilment of at least two worsening criteria defined as:

1. at least two variables fulfilling threshold criteria; or

2. at least one variable fulfilling a threshold criterion and the slopes for all variables fulfilling the slope criteria.

The occurrence of a diary event within a subject is defined as the first occasion when either (1) or (2) above occurs. For example, in the case of the algorithm for the PRS diary event defined in Table 3: this diary event is based on PEF [morning (m) and evening (e)], reliever use [morning and evening] and symptoms [morning and evening], giving six different diary variables to consider. The diary event for case (1) is defined so that the threshold deterioration criterion needs to be fulfilled for one of the PEF variables at the same time as the criterion is fulfilled for either one of the reliever or symptom variables. This gives in total eight variable combinations (Pm/Rm, Pm/Re, Pe/Rm, Pe/Re and Pm/Sm, Pm/Se, Pe/Sm, Pe/Se) where the deterioration needs to be fulfilled for both variables in at least one combination in order for a diary event to occur. The first of the two days where the threshold is reached for at least two variable is taken as the starting point of the event.
The diary event for (2) will occur when one of the six diary variables fulfils the threshold deterioration criterion at the same time as the slope criterion is fulfilled for all six variables.

The thresholds (as T1 in the reference paper) for the diary event endpoints are defined as follows:

- PEF morning/evening: ≥ 15% decrease compared to baseline
- Reliever medication (rescue) use morning/evening: increase ≥ 1.5 doses compared to baseline
- Asthma symptoms morning/evening: increase of ≥ 1 score compared to baseline or absolute score of 4
- Night-time awakening: awakening with increase in rescue use (> 0.5 doses) relative to baseline

The slopes (as S3 in the reference paper) for the diary event endpoints are defined as follows:

- PEF morning/evening: decrease rate > 3% per day
- Reliever medication (rescue) use morning/evening: increase rate > 0.3 doses per day
- Asthma symptoms morning/evening: increase rate > 0.2 scores per day
- Night-time awakening: increase rate > 0.1 doses per day

The following is an illustrative example for calculating the slope for PEF (evening):

- Fit a univariate linear regression line $y = k*x + m$

- where y = PEF change from baseline (evening), x = day, k = slope and m = intercept

Slopes are computed over 5-day intervals with the last day of the interval being the start day of the event. If there is less than 2 days with available data in an interval, slope is set to missing and the condition is not fulfilled. Thresholds are computed for 2-day intervals with the first day of the interval being the start day of the event.

Threshold diary events are defined as starting at the earliest on the start day of treatment (Day 1), with event on Days 1-2, and at the latest ending on Day 364 (event on Days 364-365).

Slope diary events (start day of treatment = Day1) are defined as starting at the earliest on Day 5 (with event on Days 1-5) and ending latest on Day 365 (with event on Days 361-365). However, if slope diary events are calculated for those days where at least one variable fulfills a threshold criterion, the last possible day for a slope diary event will be Day 364.

For subjects prematurely discontinuing, the above definitions will be amended for actual end day of treatment and actual start day of post-treatment.

Events are searched for up to the last day with entry in the diary cards. Missing values indicate no event. Missing diary data will not be imputed. If diary card entries stop prematurely (before the last day in the study) or if the patient lacks data during the period, the patient is to be censored as having no event at the last day in the period. This will be either the last day with recordings in the diary or the last day the patient was assessed for severe asthma exacerbation.

The outcome variables for CompEx events will be as follows:

- Time to first CompEx event during the 52-weeks following randomisation, for each of CompEx PR, PS, PA, PRS and PRSA

- Proportion of patients with a CompEx event during the 52-weeks following randomisation, for each of CompEx PR, PS,PA, PRS and PRSA

Table 3 Definition of diary events evaluated as possible building blocks for CompEx

Diary event	Variables	Definition
PR	P - PEF morning/evening R - Reliever morning/evening	2/2 days above threshold on PEF (morning or evening) and reliever (morning or evening), or 2/2 days above threshold on 1/4 variables + 4/4 slopes
PS	P - PEF morning/evening S - Symptoms morning/evening	2/2 days above threshold on PEF (morning or evening) and symptoms (morning or evening), or 2/2 days above threshold on 1/4 variables + 4/4 slopes
PA	P - PEF morning/evening A - Awakenings + Reliever morning	2/2 days above threshold on PEF (morning or evening) and awakenings, or 2/2 days above threshold on 1/3 variables + 3/3 slopes
PRS	P - PEF morning/evening R - Reliever morning/evening S - Symptoms morning/evening	2/2 days above threshold on PEF (morning or evening) and [reliever (morning or evening), or symptoms (morning or evening)], or 2/2 days above threshold on 1/6 variables + 6/6 slopes
PRSA	P - PEF morning/evening R - Reliever morning/evening S - Symptoms morning/evening A - Awakenings	2/2 days above threshold on PEF (morning or evening) and [reliever (morning/evening), or symptoms (morning or evening), or awakenings (with reliever morning increased)], or 2/2 days above threshold on 1/7 variables + 7/7 slopes

Abbreviations: PEF: peak expiratory flow; R: reliever use (doses); A: awakenings + morning reliever use; S: symptoms

3.5.2 Biomarker analysis

Biomarkers will be taken at study time points in accordance with the protocol.

The exploratory biomarker data will not be included in the CSR, and the analysis is not described in this SAP.

3.5.3 Pharmacogenetics research (PGx)

Data collected in the pharmacogenetics research will not be included in the CSR, and the analysis is not described in this SAP.

3.5.4 Pharmacodynamics research (PD)

Data collected in the pharmacodynamics research will not be included in the CSR, and the analysis is not described in this SAP.

3.5.5 Sputum Induction

Data collected in the sputum induction research will not be included in the CSR, and the analysis is not described in this SAP.

4. ANALYSIS METHODS

4.1 General principles

The analysis of the study outcome variables will include all data captured during the 52-week double blind treatment and follow-up period. This includes data regardless of whether IP was prematurely discontinued or delayed, and/or irrespective of protocol adherence, unless the patient withdraws consent or assent to study participation.

A summary table which counts patients who have been incorrectly randomised and who received incorrect treatment will be presented.

Summary data will be presented in tabular format by treatment. Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables for parametric data will be summarized by descriptive statistics including N, mean, (standard deviation) SD, median, and range.

Minimum and maximum values will be reported to the same degree of precision as the raw data unless otherwise stated. Mean, median, SD, confidence intervals (CIs), geometric mean and CV will be reported to one further degree of precision. Percentage frequencies will be presented to one decimal place.

Given the number of endpoints in the secondary analyses, multiplicity procedures will not be used to attempt to control ‘alpha’ across all secondary endpoints.

All data will be listed. Data listings will be sorted by treatment and subject number. Summaries by visit will include baseline but not visits intended for screening and randomisation.

All hypothesis testing will be reported using 2-sided tests except for the primary analysis which will be 1-sided and the p-value will be presented to 4 decimal places. Where confidence

intervals (CI) are presented for treatment comparisons these will be presented as 2-sided 95% CIs.

Plots of data by visit or visit window will cover the entire study period including follow-up.

4.2 Analysis methods

4.2.1 Patient disposition, demography data and patients characteristics

Patient disposition will be summarized using the All Patient analysis set.

The number of enrolled patients will be summarized. The number and percentage of patients within each treatment group will be presented by the following categories; randomised, not randomised (and reason), received study treatment, did not receive study treatment (and reason), completed treatment, discontinued treatment (and reason), completed study, and discontinued study (including reason).

The number and percentage of patients, who discontinued IP, but remained in the study will be presented by treatment group. Kaplan-Meier plots will be produced summarizing the time (in days) to discontinuation of IP and withdrawal from the study.

Demographic data such as age, gender, race and ethnicity will be summarized by treatment group for the FAS.

Various baseline characteristics will also be summarized by treatment for the FAS. These include weight, height, body mass index (BMI), medical, surgical and respiratory disease histories, history of allergic rhinitis, FEV_1 (pre and post-BD) at baseline, age at onset of asthma, asthma duration, the number of asthma exacerbations in the previous 12 months, the number of asthma exacerbations requiring hospitalizations in the previous 12 months, number of exacerbations resulting in antibiotic treatment, type of recent exacerbations, the number of admissions to ICU (Intensive Care Unit) for asthma during the hospitalization, eosinophil count, smoking status, nicotine consumption, reversibility test.

The following covariates are deemed to be of interest for inclusion in the statistical models of the primary and secondary endpoints. Possible covariates include but are not limited to: age at first asthma allergy status, whether hospitalized within the last year, race, sex, baseline spirometry variable measurements, baseline PEF, baseline ACQ-5 and baseline asthma symptom scores. For Blinded Deliverable review analyses, the following five covariates have been selected: age, race, sex, age at first asthma allergy status and whether hospitalized within the last year. For the final analysis, only age and gender will be included as covariates in the statistical models.

Medical and surgical histories will be summarized by using the latest version of MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA. For medical history, conditions are identified as current or past in the eCRF HISM page. Surgical history is specified in the HISS eCRF page.

4.2.2 Prior and Concomitant Medications

The number and percentage of patients who had prior medications and take concomitant medications will be presented by treatment group for the FAS. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary. The summary tables will present medications by generic term using Anatomical Therapeutic Chemical (ATC) classification system codes.

Separate tables will be presented for all medications received during the following periods

- Prior: Medications with a start and stop date before Visit 2 date (first day of IP). If the stop date is missing or partial and it cannot be determined whether the subject stopped the drug before the start of study medication, the medication will be considered as concomitant.

- Concomitant medications while on treatment: Medications with start date ≤ the last day of IP and stop date ≥ the first day of IP. If the start or stop date is missing or partial and cannot be determined, the medication will be considered as concomitant. If the medication started whilst on IP and was ongoing (no stop date) then this is also a concomitant medication.

- Concomitant medications during follow-up: Medications categorised as 'Concomitant' that are still ongoing one day after the last day of IP, and also

    - Medications with start date > last day of IP and ≤ date of Visit 21; this is only applicable for subjects that are treated for the entire treatment period

    - Medications with start date > last day of IP and ≤ the last day of IP + 1 week; this is only applicable for subjects that prematurely discontinue IP

Previous disease-related treatments will also be tabulated.

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose of ICS and LABA. The number of patients using other maintenance asthma medications at baseline will also be summarised. In addition, the total number of days of oral glucocorticosteroid treatment associated with asthma exacerbations per patient from the first day of IP up to Week 52 will also be summarised.

Medications will be classified according to the AstraZeneca Drug Dictionary (AZDD). Percentages will be calculated relative to the number of patients in the FAS.

Data from patients who discontinued IP, where possible and relevant, be included in the appropriate medication summaries.

4.2.3 Exposure and Compliance

Extent of exposure to IP by compliance, total treatment duration by mean daily dose, and recordings on eDiary will be summarized by treatment group and using both the safety analysis set and full analysis set.

The date and time of all IP administrations, and all missed doses will be listed using the safety analysis set.

4.2.3.1 Exposure

Extent of exposure to IP is defined as the number of days between the start and the end dates of study therapy:

Extent of exposure (days) = (Last dosing date +7 days) - first dosing date + 1.

Dosing period of IP is up to and including week 12, i.e. there is a maximum of 13 weekly doses. The calculation for study treatment exposure is consistent across all patients including those who prematurely discontinued. Expected dosing administrations can be determined by number of weeks from first dose to discontinuation.

Extent of therapy summaries will be provided for the safety and FAS analysis sets. The numbers and percentages of subjects falling into each category will be presented for each treatment group, presenting N, mean, SD, median and range.

4.2.3.2 Compliance

Compliance will be summarized for each treatment group, presenting mean, standard deviation, 1st quartile, median, 3rd quartile, and range. In addition, the following compliance categories will be derived: <80%, 80% -120%, >120%The numbers and percentages of subjects falling into each category will be presented for each treatment group. Missing responses will not be imputed. Data collected prior to Visit 2 (Week 0) will not be included in the compliance calculations.

In addition, the total number of dosing administrations will be calculated per patient. The maximum number of possible dosing administrations for IP is 13. If the patient withdraws from the study before the 12 week dosing period is completed, the total number of dosing administrations expected depends on the duration of the patient in the study. Compliance is defined as:

Compliance (%) = (Number of dosing administrations made/number of dosing administrations expected) x 100

Compliance for PEF

The PEF will be monitored morning and evening. Patients will perform 3 successive peak flow manoeuvres while sitting or standing, capturing the highest value for morning and

evening manoeuvres. Protocol states that Investigator will check patient's adherence to correct use of the hand-held spirometer at each visit.

Compliance (%) = (Number of recordings made /number PEF recordings expected) x 100

If a patient completes the 52 weeks of the study, they would be expected to have a maximum of 2 recordings per day for 365 days i.e. 730 recordings. If the patient withdraws from the study early, the total number PEF recordings expected is based on the duration of the patient in the study.

Compliance for FeNO

Although FeNO is measured by patients using the NIOX Vero device once in the morning every second day as well as at the clinic at designated visits, compliance will be calculated using the recordings from the NIOX Vero device at home only.

Compliance (%) = *(Number of recordings made/number FeNO recording expected) x 100*

If a patient completes the 52 weeks of the study, they would be expected to have a maximum of 1 recording every other day for 365 days i.e. 183 recordings. If the patient withdraws from the study early, the total number FeNO home recordings expected is based on the duration of the patient in the study.

Compliance for eDiary

The ePRO device is used by the patients to record various measurements twice a day, morning and evening as well as night-time awakenings once every day.

Compliance (%) = *(Number of recordings made /number recordings expected) x 100*

If a patient completes the 52 weeks of the study, they would be expected to have a maximum of 2 recordings per day for 365 days i.e. 730 recordings. If the patient withdraws from the study early, the total number eDiary recordings expected is based on the duration of the patient in the study.

Compliance for ACQ-5

ACQ-5 will be self-administered within the ePRO once weekly during the study. Compliance is based on the Overall ACQ-5 Score.

Compliance (%) = *(Number of Overall ACQ-5 scores recorded/number of Overall ACQ-5 scores expected) x 100*

If a patient completes the 52 weeks of the study, they would be expected to have a maximum of 52 ACQ-5 scores. If the patient withdraws from the study early, the total number ACQ-5 scores expected is based on the duration of the patient in the study.

4.2.4 Analysis of the primary variable

Under a proportional hazard assumption, we can define the hazard ratio as $\theta = H_A(t)/H_B(t)$ for all $t \leq \tau$, τ is the largest observation time. A represents the active treatment arm (AZD1419), B represents placebo and H(t) is the hazard function. To compare the effect of active treatment AZD1419 to placebo group, a log-rank (Mantel-Cox χ^2) test will be carried out using the SAS® procedure PROC LIFETEST, where the null hypotheses will be:

H_0: $\theta = 1$

H_1: $\theta < 1$

The null hypothesis (H_0) is that during the 52-week double-blind treatment period, the time to loss of asthma control in the AZD1419 arm is equal to the corresponding time to loss of asthma control in the placebo arm. The alternative hypothesis (H_1) is that the time to loss of asthma control in the active arm (AZD1419) is longer than in the placebo arm.

Time to loss of asthma control will be displayed graphically using a Kaplan-Meier plot (time axis, will be time from randomisation).

A Cox proportional hazard model will be fitted to the data to compare the treatments using the SAS® procedure PROC PHREG. Results of the analysis will be summarized as hazard ratio, 2-sided 95% confidence interval and p-value comparing AZD1419 with placebo. The hypothesis test will be 1-sided, with alpha=0.05. The covariates for inclusion in the statistical model are described in Section 4.2.1.

For patients who withdraw from the study without reporting loss of asthma control, time will be censored at the date of withdrawal, if known, else at the patient's last clinical visit plus one day.

The assumptions underlying the statistical model will be explored. If the proportional hazards assumption does not hold then alternative methods will be explored which may include the following:1) Extend the model to include exposure-time interaction term or 2) if the variable for which there is evidence of non-proportional hazards is a confounder, rather than the main exposure of interest then regression may be stratified.

Sensitivity analysis will be performed on the primary variable, see Section 5.1.

4.2.4.1 Loss of asthma control as group proportions

The proportion of patients with loss of asthma control will be compared between the two treatment groups at each clinical visit, using a generalized linear model based on a generalized estimating equations (GEE) approach, with occurrence of any loss of control as a binary outcome variable. Treatment group and visit will be included as factors in the model. The covariates for inclusion in the statistical model are described in Section 4.2.1. If a patient had

a 'loss of asthma control' event at one visit, the subsequent visits information should be removed. Each patient can only be counted once towards 'loss of asthma control'.

This analysis will be carried out using a log-binomial regression model using PROC GLIMMIX in SAS with a random subject effect. The estimated treatment effect (i.e. the rate ratio of AZD1419 versus placebo), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented.

In the case that If the GEE model fails to converge, due to the estimation method not being Restricted Maximum Likelihood (REML), then only the Mixed Model will be explored. The variance-covariance will be assumed to be unstructured. other options will be explored e.g. using the PROC GLIMMIX procedure in SAS. For PROC GLIMMIX, initially this will be fitted with a random statement fitting a random intercept and a Laplace approximation for maximum likelihood estimation. Again, to facilitate convergence, one or more of the covariates could be removed leaving the basic model. In case this model also fails to converge, the random statement will be removed which will result in a conventional logistic regression model being fitted.

The assumptions underlying the statistical model will be explored. If assumptions do not hold, then alternative strategies will be considered.

Summary statistics will also be presented for each treatment group at each visit.

4.2.4.2 Analysis of ACQ-5

Weekly average ACQ-5 score will be summarized by absolute score at each week by treatment group, together with the corresponding changes from baseline. Summaries will be descriptive statistics including N, mean, SD, median and range.

Weekly average ACQ-5 will be analysed longitudinally, using a mixed effects model for repeated measures (MMRM). Fixed categorical effects of treatment group and week will be included in the model with patient as a random effect. The baseline covariate will be the unweighted mean of the 5 questions at Visit 2 (Week 0). Further covariates for inclusion in the statistical model are described in Section 4.2.1. At each week, all observed values will be used in this analysis. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

$$\textit{Weekly average in } ACQ_{ijk} = \textit{Treatment group}_i + \textit{baseline } ACQ_k + \textit{week}_j + \textit{treatment}_i * \textit{week}_j + \textit{random patient effect}_k + \textit{covariates}_k; \textit{ (where i=treatment group, j=week and k=patient).}$$

Results will be presented for each timepoint and overall in terms of LSMEANS, treatment differences in LSMEANS, 95% confidence intervals and p-values.

The assumptions underlying the statistical model will be explored. If assumptions do not hold, then alternative strategies will be considered including transformation of the response variable or analysing the data using a non-parametric method.

4.2.4.3 Asthma daily diary score

Weekly average Asthma daily diary score will be analysed using the same method, MMRM as described in Section 4.2.4.2.

Weekly average in Asthma daily diary$_{ijk}$ = *Treatment group*$_i$ + *baseline asthma daily diary score*$_k$ + *week*$_j$ + *treatment*$_i$**week*$_j$ + *random patient effect*$_k$ + *covariates*$_k$; *(w*here i=treatment group,j=week and k=patient).

Results will be presented for each timepoint and overall in terms of LSMEANS, treatment differences in LSMEANS, 95% CI and p-values.

The assumptions underlying the statistical model will be explored. If assumptions do not hold, then alternative strategies will be considered as described in Section 4.2.4.2.

Summary statistics for Asthma Daily Diary will be produced by treatment group over time for the weekly average and the change from baseline in weekly average. Daytime and night-time scores will be similarly summarized as well as total.

4.2.4.4 Reliever Bronchodilator (Use of SABA)

Responder variable Reliever Bronchodilator (yes/no) will be analysed using a logistic regression model with responder at Week 52 as the response variable and covariates of treatment and week. Further covariates for inclusion in the statistical model are described in Section 4.2.4.2. The results of the analyses will be presented as odds ratios with associated 95% CI and 2-sided p-value.

The assumptions underlying the statistical model will be explored. If assumptions do not hold, then alternative strategies will be considered.

Summary statistics will be produced for the Reliever medication for each treatment group over time for the weekly average and the change from baseline in weekly average. A sensitivity summary table is also described for this variable in Section 5.1.

4.2.4.5 Forced expiratory volume in 1 second (FEV_1)

FEV_1 is measured at each clinical visit. FEV_1 will be analysed at each visit longitudinally separately for FEV_1 pre-dose/pre-BD and FEV_1 pre-dose/post-BD, using the same method, MMRM as described in Section 4.2.4.2.

FEV$_{ijk}$ = *Treatment group*$_i$ +*baseline FEV*$_{1k}$ + *visit*$_j$ + *treatment*$_j$**visit*$_j$ + *random patient effect*$_k$ + *covariates*$_k$; *(where i=treatment group, j=visit and k=patient.)*

The pre-dose/pre-BD baseline FEV_1 covariate will be used in the pre-dose/pre-BD model. The pre-dose/post-BD baseline FEV_1 covariate will be used in the pre-dose/post-BD model. Results will be presented for each timepoint and overall in terms of LSMEANS, treatment differences in LSMEANS, 95% confidence intervals and p-values.

The assumptions underlying the statistical model will be explored. If assumptions do not hold, then alternative strategies will be considered as described in Section 4.2.4.2.

Summary statistics will be presented for each treatment group at each visit for pre-dose/pre-BD FEV_1 and pre-dose/post-BD FEV_1. The absolute score at each planned visit by treatment group, together with the corresponding changes from baseline will be summarised. Summaries will be descriptive statistics including N, mean, SD, median and range.

4.2.4.6 Peak expiratory flow (PEF)

PEF is measured daily using the ePRO device. For the purposes of summary and analysis, a weekly average PEF will be computed.

Weekly average PEF will be analysed longitudinally, using MMRM as described in Section 4.2.4.2.

$Weekly\ average\ in\ PEF_{ijk} = Treatment\ group_i + baseline\ PEF_k + week_j + treatment_i{*}week_j + random\ patient\ effect_k + covariates_k$; (where i=treatment group, j=week and k=patient).

Results will be presented for each timepoint and overall in terms of LSMEANS, treatment differences in LSMEANS, 95% CI and p-values.

The assumptions underlying the statistical model will be explored. If assumptions do not hold, then alternative strategies will be considered as described in Section 4.2.4.2.

Summary statistics for PEF will be produced by treatment group over time for the weekly average and the change from baseline in weekly average, as well as morning weekly average and evenings weekly average. Summaries will be descriptive statistics including N, mean, SD, median and range.

4.2.4.7 Analysis of fractional exhaled nitric oxide (FeNO)

FeNO is measured using the NIOX Vero® device every other day as well as at clinical visits.

For the purposes of summary and analysis, a weekly average FeNO will be computed.

Weekly FeNO will be analysed longitudinally, using MMRM as described in Section 4.2.4.2.

$Weekly\ average\ in\ FeNO_{ijk} = Treatment\ group_i + baseline\ FeNO_k + week_j + treatment_i{*}week_j + random\ patient\ effect_k + covariates_k$; (where i=treatment group, j=week and k=patient).

Results will be presented for each timepoint and overall in terms of LSMEANS, treatment differences in LSMEANS, 95% CI and p-values.

Summary statistics for FeNO will be produced by treatment group over time for the weekly average and the change from baseline in weekly average. Summaries will be descriptive statistics including N, mean, SD, median and range.

4.2.4.8 Time to moderate or severe exacerbation

The null hypothesis, that the time to moderate or severe exacerbation is not different between AZD1419 and placebo groups, will be tested using the log rank test (with Kaplan Meier plot) as discussed in Section 4.2.4.

A Cox proportional hazard model will be fitted to the data using the SAS® procedure PROC PHREG, results of the analysis will be summarized as hazard ratio, 2-sided 95% CI and p-values comparing AZD1419 with placebo. The hypothesis test will be 2-sided, with alpha=0.05.

Time to moderate or severe exacerbation will be censored at 52 weeks for patients who do not experience loss of asthma control during the 52-week study period.

For patients who withdrew from the study without reporting moderate or severe exacerbation, time will be censored at the date of withdrawal, if known, else at the patients last clinical visit plus one day.

The assumptions underlying the statistical model will be explored. If the proportional hazards assumption does not hold, then alternative strategies will be considered as described in Section 4.2.4.

4.2.4.9 Proportion of patients with a moderate or severe asthma exacerbation

The proportion of patients with an asthma exacerbation will be compared between the two treatment groups at each clinical visit, using a generalized linear model based on a generalized estimating equations (GEE) approach as described in Section 4.2.4.1, with occurrence of exacerbation since the start of treatment as a binary outcome variable.

4.2.4.10 FVC and FEF25-75

Summary statistics, including N, mean SD, median and range will also be presented for each treatment group at each visit.

4.2.4.11 Night time awakenings

Weekly mean number (percentage) of nights with awakening due to asthma will be summarised by descriptive statistics including N, mean, SD, median, and range.

4.2.4.12 Data collected at Sentinel Dosing procedures

Efficacy data collected during the sentinel dosing procedure (IC, FEV_1/FVC ratio, PEF, DLco, FeNO, Forced Expiratory Flow 25%, Forced Expiratory Flow 75%, Forced Expiratory Flow 25% to 75% (FEF25-75%), FEV_1 and VC) at timepoints 0.5, 1,2, 6, 12 and 24 hours will not be included in descriptive summaries or any statistical analysis. This data will be listed only.

4.2.5 Safety analysis

All safety variables will be summarized by treatment received and evaluated descriptively utilizing the safety analysis set. No formal hypothesis testing of safety data is planned.

4.2.5.1 Adverse events

All AEs recorded in the eCRF will be coded according to the terminology of the latest version of MedDRA. AEs may be based on signs and symptoms or may be based on examinations and tests as described in Sections 6.3.5 and 6.3.6 of the protocol respectively.

An overall summary table will be produced showing the number and percentage of subjects with at least 1 AE in any of the following categories: AE, serious adverse events (SAEs), deaths due to AE and AEs causing discontinuation of IP (DAEs). The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e., accounting for multiple occurrences of the same event in a subject).
AEs will be summarised by SOC and PT. For each PT, the number and percentage of subjects reporting at least one occurrence will be presented i.e. for a subject multiple occurrences of an AE will only be counted once.

AEs (by PT) will be summarised by causality and maximum intensity. If a subject reports multiple occurrences of the same AE, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate and severe). A missing intensity will be considered as severe and a missing causal relationship to IP will be considered as related.

The following will also be summarised by SOC and PT: SAEs; DAEs; most common AE's (frequency of >5%) (by PT only); and AEs with outcome of deaths.

Treatment-emergent AEs will be tabulated (number and percentage of patients) by system organ class, preferred term (PT), intensity, and relation to IP according to the treatment actually received.

Adverse events will be summarized separately for the following periods: AEs occurring during pre-treatment, AEs occurring during study, AEs occurring during ICS+LABA treatment period, AEs occurring during ICS taper down period and AEs occurring during remainder of study as defined in Section 3.4.1.

Summary tables will also be produced showing Flu-like Adverse Events by preferred term, relationship to treatment and severity. The number and percentage of subjects with at least 1

Flu-like AE will be displayed as well as the total number of AEs for each preferred term by maximum reported intensity. Separate tables will be presented for each of the following periods: AEs occurring during study, AEs occurring during ICS+LABA treatment period, AEs occurring during ICS taper down period and AEs occurring during remainder of study as defined in Section 3.4.1. A table will also be presented for the AEs occurring during IP only treatment period. This is defined as

- *AEs occurring during IP only treatment period (onset date ≥ Visit 11 (Week 9) < Visit 15 (Week 13))*

Flu-like symptoms are defined as events of arthralgia, chills, pyrexia (fever), or myalgia (see section 6.1.1 of protocol).

4.2.5.2 Laboratory data

All continuous laboratory parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted by treatment group.

Central (or local) laboratory reference ranges will be used for the identification of individual clinically important abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing values. The shift tables will present baseline and last on-treatment value for each parameter. On-treatment is defined from date of first dose and including visit 14 (week 12).

Shift plots showing each individual subject's laboratory value at baseline and at the last on-treatment value will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points, then shift plots of these data may be produced. A diagonal line indicating no change, and horizontal and vertical reference lines indicating the limits of the central (or local) laboratory reference ranges will also be displayed on the shift plots.

Data for subjects who have treatment-emergent changes outside predefined criteria will be presented. This data presentation will include all visits for this subset of subjects. A change is treatment-emergent if it occurred during treatment, from the date of first dose of randomised treatment up to and including the follow-up period.

The frequency of treatment-emergent changes outside predefined criteria between baseline and each post-treatment time point will be tabulated

In order to identify potential Hy's Law cases, maximum post baseline TBL will be plotted against maximum post baseline ALT, expressed as multiples of ULN. This plot will be repeated to show maximum post baseline TBL against maximum post baseline AST, expressed as multiples of ULN. These plots will be produced on a log scale and reference lines will be included at 2xULN for TBL and at 3xULN for ALT/AST.

For all subjects who meet the biochemical criteria for Hy's law (potential Hy's Law), a Subject Safety Narrative will be produced, and the relevant laboratory parameters will be tabulated showing all visits for these subjects. Subjects with elevated ALT or AST, and elevated TBL, at any time may be explored further graphically using individual subject profile plots.

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

4.2.5.3 Vital signs

All vital signs parameters will be summarized by absolute value at each visit by treatment group, together with the corresponding changes from baseline. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum mean and SD.

AstraZeneca defined reference ranges will be used for the identification of individual abnormalities, and a shift table will be produced for each vital signs parameter to display low, normal, high, and missing values. The shift tables will present baseline and maximum/minimum during treatment value, as applicable for each parameter.

Shift plots showing each individual subject's vital signs value at baseline and at maximum/minimum will be produced for each continuous vital signs parameter.

Data for subjects who have treatment-emergent changes outside the predefined criteria will be presented, using AstraZeneca clinically important change criteria. This data presentation will include all visits for each parameter with treatment-emergent changes for this subset of subjects. A change is treatment-emergent if it occurred on study as defined in Section 3.4.1.

Data collected during the Sentinel visits will not be included as part of the summary statistics calculations or shift plots and will not be flagged, However, all recorded vital signs data will be listed.

4.2.5.4 Diffusing Capacity of the Lung for Carbon Monoxide (DLco)

DLco at each visit for which it is recorded will be summarized by treatment group with descriptive statistics.

4.2.5.5 ECG

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

A shift table will be produced showing the change between baseline and the end of study assessment.

Absolute values and change from baseline for ECG parameters RR, PR, QRS and heart rate reported by the central ECG laboratory will be summarized by visit. The reference ranges are presented in Table 4.

Table 4 ECG reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
ECG Heart rate	Beats/min	<60	>100
RR interval	ms	<60	>100
PR interval	ms	<120	>200
QRS duration	ms	<60	>120

4.2.5.6 Physical examination

Shift tables (normal, abnormal (same as baseline, new or aggravated)) of baseline versus last on-treatment observation will be generated, presenting the assessment for each component of the complete physical examination separately. Listings of abnormal results will be produced.

4.2.5.7 Composite endpoint for exacerbations (CompEx)

Time to (first) CompEx event, for each of the five variants of CompEx, will be compared between AZD1419 and Placebo using a Cox proportional hazard model adjusting for treatment group. The hypothesis test will be 2-sided, with alpha=0.05.

Data will be visualized using Kaplan-Meier plots.

The proportion of subject's with CompEx events will be compared between treatments using a log-binomial regression model. Treatment group will be included as a factor in the model. The back-transformed estimated treatment effect (i.e. the ratio of proportions, AZD1419 over placebo, will be presented with 2-sided 95% confidence interval and p-value (2-sided alternative). The model will be fitted using the SAS® procedure PROC GLIMMIX as described in Section 4.2.4.1.

5. INTERIM ANALYSES

A purely Administrative Interim analysis (IA) will be conducted internally at AZ with no consequences for the trial. Therefore, the details of the IA are outside the scope of the SAP, as no interim outputs will be provided in the CSR.

5.1 Sensitivity analysis

An analysis will be conducted on the primary outcome variable, loss of asthma control, using the same log rank test as for the primary analysis, but making the assumption that all patients who withdraw from the study without recorded loss of control are classed as loss of control (instead of being censored), in order to test the sensitivity of the results to the use of censoring/lack of information regarding loss of control in patients who withdraw.

Summary statistics will be produced for the reliever medication for each treatment group over time for the weekly average and the change from baseline in weekly average by 1) imputing missing values to zero and 2) imputing using last observation carried forward (LOCF) method.

Summary statistics will be produced for Asthma Symptom scores (weekly total: mean total daily score, number of asthma symptom free days and proportion of asthma symptom free days endpoints) for each treatment group over time for the weekly average by 1) imputing missing values to zero and 2) imputing using last observation carried forward (LOCF) method.

For LOCF, the missing values will be populated until the patient has their next non-missing value or until the patient either completes the study or withdraws from the study. For both imputation methods, the individual missing values should be imputed (not daily sums or weekly averages).

6. CHANGES OF ANALYSIS FROM PROTOCOL

Updated detail to categorization of AE data.

Additional Cox proportional hazards model added for loss of asthma control for the primary endpoint

Additional Cox proportional hazards model added for time to first moderate or severe exacerbation as a secondary endpoint.

Additional summary statistics for asthma daily diary score

Additional logistic regression analysis added to the analysis of reliever bronchodilator

Updated detail to the analysis of CompEx, using a Cox hazard model, and a log binomial regression model as well as Kaplan Meier plots.

Updated statistical models for ACQ-5, Asthma Daily Diary score, PEF and FeNO to add a treatment*week interaction term.

Additional summary statistics for PEF.

Choice of covariates described for Blinded Deliverable review analyses and final analysis.

Summary statistics for time to loss of asthma control added.

Sensitivity summary statistics proposed for Reliever Medication and Asthma Symptom scores.

Changed a secondary endpoint definition from ‘proportion of patients who experience ≥1 moderate or severe exacerbation during the 52-weeks of treatment’ to ‘proportion of patients who experience 1 moderate or severe exacerbation during the 52-weeks of treatment’.

Clarified the time to event analysis for ‘moderate or severe exacerbation’.

Clarified the FAS definition to remove ambiguity. Patients that ‘did not take IP’ will not be in the FAS.

7. REFERENCES

Fuhlbrigge et al 2017

Fuhlbrigge, AL, Bengtsson T, Peterson S, Jauhiainen A, Eriksson G, Da Silva CA, Johnson A, Sethi T, Locantore N, Tal-Singer R, Fagerås M. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. Lancet Respir Med 2017;5:577–90

8. APPENDIX

8.1 Appendix A Analysis windows

Table 5 Analysis windows for weekly summaries

Week	Adjusted windows for weekly measures using morning or daily assessments	Adjusted windows for weekly measures using evening assessments
1	2-8	1-7
2	9-15	8-14
3	16-22	15-21
4	23-29	22-28
5	30-36	29-35
6	37-43	36-42
7	44-50	43-49
8	51-57	50-56
9	58-64	57-63
10	65-71	64-70
11	72-78	71-77
12	79-85	78-84
13	86-92	85-91
14	93-99	92-98
15	100-106	99-105
16	107-113	106-112
17	114-120	113-119
18	121-127	120-126
19	128-134	127-133
20	135-141	134-140
21	142-148	141-147
22	149-155	148-154
23	156-162	155-161

Week	Adjusted windows for weekly measures using morning or daily assessments	Adjusted windows for weekly measures using evening assessments
24	163-169	162-168
25	170-176	169-175
26	177-183	176-182
27	184-190	183-189
28	191-197	190-196
29	198-204	197-203
30	205-211	204-210
31	212-218	211-217
32	219-225	218-224
33	226-232	225-231
34	233-239	232-238
35	240-246	239-245
36	247-253	246-252
37	254-260	253-259
38	261-267	260-266
39	268-274	267-273
40	275-281	274-280
41	282-288	281-287
42	289-295	288-294
43	296-302	295-301
44	303-309	302-308
45	310-316	309-315
46	317-323	316-322
47	324-330	323-329
48	331-337	330-336
49	338-344	337-343
50	345-351	344-350
51	352-358	351-357
52	359-365	358-364

Table 6 Analysis windows for scheduled visits

Visit	Target Day	Adjusted windows for scheduled visits
Visit 2 (Week 0)*	1	1 - 4
Visit 3 (Week 1)	8	5-11
Visit 4 (Week 2)	15	12-18
Visit 5 (Week 3)	22	19-25
Visit 6 (Week 4)	29	26-32
Visit 7 (Week 5)	36	33-39
Visit 8 (Week 6)	43	40-46
Visit 9 (Week 7)	50	47-53
Visit 10 (Week 8)	57	54-60
Visit 11 (Week 9)	64	61-67
Visit 12 (Week 10)	71	68-74
Visit 13 (Week 11)	78	75-81
Visit 14 (Week 12)	85	82-88
Visit 15 (Week 13)	99	89-109
Visit 16 (Week 16)	113	110-127
Visit 17 (Week 20)	141	128-169
Visit 18 (Week 28)	197	170-225
Visit 19 (Week 36)	253	226-295
Visit 20 (Week 48)	337	296-351
Visit 21 (Week 52)	365	352-375

*Prior to first dose/randomisation, visits will be assigned to the Nominal visit. The visit windows will be applied thereafter.