Parexel International

AstraZeneca

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A Two-part Phase IIa Randomised, Double-blind, Placebo-controlled, Dose-ranging, Multi-centre Study to Assess Efficacy and Safety of Inhaled AZD1402 Administered as a Dry Powder Twice Daily for Four Weeks in Adults with Asthma on Medium-to-High Dose Inhaled Corticosteroids

Statistical Analysis Plan

Version: 5.0

Parexel Project Number: 248066

SPONSOR SIGNATURE PAGE

Approved by:

PPD	Date
PPD	
AstraZeneca	

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	03 Dec 2020	New document
Draft 0.2	29 March 2021	Updated with AstraZeneca (AZ) comments
Draft 0.3	20 April 2021	Updated after Comment Resolution meeting (CRM)
Final 1.0	26 April 2021	Updated after AZ final review
Final 2.0	25 November 2021	Statistical Analysis Plan (SAP) approved and finalised before the Safety Review Committee (SRC) n. 1: Updated to align with the new AZ standards and for the programming requirements of the SRC.
Final 3.0	05 July 2022	SAP updated to align with Version 5.0 and 6.0 of the Protocol, updating the new standards and some baseline definitions. Two endpoints had been removed: • Change from baseline in post-bronchodilator FEV_1 average over the 4-week Treatment Period (Visit 3-Visit 7) • Change from baseline in post-bronchodilator FEV_1 at Week 2 (Visit 5)
Final 4.0	Last Signature	SAP updated to align with Protocol version 7.0.
Final 5.0	Last Signature	SAP updated for anticipated closure to remove some of the exploratory endpoints, the Per Protocol analysis and subgroup analysis. In addition the AE tables were presented for all the AEs after IP and by ADA status. The table including the number and percentage of subjects with a change from baseline in hsCRP higher then 5 and 10 mg/dL by ADA category and the Figure for hsCRP by week by ADA status and by treatment group will be also presented.

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase/transaminase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase/transaminase
ATC	Anatomical therapeutic chemical
AUClast	Area under the serum concentration-curve from zero to the last quantifiable concentration
AUCτ	Area under serum concentration-time curve in the dosing interval
BDRM	Blind data review meeting
BID	Bis in die (twice daily)
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent total body clearance of drug from serum after extravascular administration
CRF	Case Report Form
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
Cmax	Maximum observed (peak) serum concentration
CS	Clinically significant
Ctrough	Concentration immediately prior to dosing
CV	Coefficient of variation
DBP	Diastolic blood pressure

Abbreviation/Acronym	Definition/Expansion
DPI	Dry powder inhaler
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EN	Enrolled analysis set
FAS	Full analysis set
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GeoCV	Geometric coefficient of variation
GeoLSMeans	Geometric LS means
gSD	Geometric SD
CCI	CCI
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL	Interleuken
IP	Investigational Product
IPD	Important protocol deviations
IS	Immunogenicity set
LABA	Long-acting beta-adrenoceptor agonists
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation/Acronym	Definition/Expansion
MMRM	Mixed model repeated measure
NA	Not applicable
NCS	Not clinically significant
ND	Not determined
NR	Not reportable
NS	No sample
CCI	CCI
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDF	Portable document format
PEF	Peak expiratory flow
PK	Pharmacokinetic
PPS	Per protocol set
PRO	Patient Reported Outcomes
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T-wave
QTcB interval	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
Rac	Drug accumulation ratio
RS	Randomised set
SABA	Short-acting beta agonist
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error of the mean
SoA	Schedule of Assessments
SOC	System Organ Class
SPFQ	Study Participant Feedback Questionnaire

Abbreviation/Acronym	Definition/Expansion
SRC	Safety Review Committee
SS	Safety set
t	Time of last observed (quantifiable) concentration
t1/2λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
TB	Tuberculosis
TFLs	Tables, Figures, and Listings
tmax	Time to reach peak or maximum observed concentration
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
URC	Unblinded Review Committee
VAS	Visual Analogue Scale
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)
WHO-DD	World Health Organization Drug Dictionary
WNL	WinNonlin
λz	Terminal elimination rate constant

1 INTRODUCTION

Inhaled corticosteroids are considered the "gold standard" in controlling asthma symptoms and long-acting beta agonists (LABAs) are the most effective bronchodilators currently available. These agents are often given in combination as research has demonstrated that combination therapy of an inhaled corticosteroid (ICS) with an inhaled LABA provides better asthma control than high doses of ICS alone. It is estimated that 5% to 10% of the population with asthma has symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. For those moderate/severe asthma participants that remain uncontrolled on currently approved inhaled or oral treatments there is a clear unmet need for new therapies before introducing systemic biologic treatment. Inhaled drugs are advantageous as the drug delivery is localised to the lung (target organ) which may allow for a lower dose than needed with systemic delivery. Inhalation is also non-invasive, and thus offers advantages in terms of ease of use. Current research is focusing on the different pathological mechanisms or endotypes of severe asthma and it is anticipated that this will lead to the development of effective therapies for these subsets of asthma patients. AZD1402 is being developed as an inhaled interleukin (IL-)4Rα antagonist controller therapy for the treatment of moderate to severe persistent asthma in participants who are not adequately controlled on standard of care therapies. The current study aims to assess the efficacy and safety of inhaled AZD1402 administered via dry powder inhaler (DPI) CCI [redacted] CCI [redacted] for 4 weeks in adults with asthma on medium-to-high dose ICS in a 2-part randomised, double-blind, placebo-controlled, and multi-centre study.

This Statistical Analysis Plan (SAP) details the statistical methodology to be used for analysing the study data and outlines the statistical programming specifications for the tables, figures, and listings (TFLs). It describes the variables and analysis sets, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP).
The SAP describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. Any deviations after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP addendum and discussed in the Clinical Study Report (CSR). Any changes to this SAP prior to database lock will be described in a new version of the SAP.

The following endpoints will be reported outside of the CSR and are therefore outside of the scope of this SAP:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 8.0 (24 March 2023).
- Annotated Case Report Form 1.0 (21 January 2021).
- Annotated Case Report Form updates 7.0 (16 February 2023)

2 STUDY OBJECTIVES

2.1 Part 1 Objectives

2.1.1 Primary Objective

The primary objective in Part 1 of the study is to evaluate the safety and tolerability of AZD1402 compared to placebo at different dose levels in adults with asthma controlled on medium-to-high dose ICS-LABA.

2.1.2 Secondary Objective

The secondary objective in Part 1 of the study is to investigate the pharmacokinetic (PK) profile and immunogenicity of AZD1402, and associated effects on safety.

2.1.3 Exploratory Objectives

The exploratory objectives in Part 1 are:

i) CCI [redacted]

ii) To assess the effect of AZD1402 compared to placebo on cough by a Visual Analogue Scale (VAS) in adults with asthma controlled on medium dose ICS-LABA.

iii) CCI [redacted]

iv) CCI [redacted]

v) CCI [redacted]

Note that, the exploratory objectives iii), iv), and v) described above will not be presented as part of the final CSR, therefore, they are not part of this SAP.

2.2 Part 2 Objectives

2.2.1 Primary Objective

The primary objective in Part 2 of the study is to investigate the efficacy of inhaled AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA.

2.2.2 Secondary Objective

The secondary objectives in Part 2 are:

i) To further investigate the efficacy of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA.

ii) To investigate the effect of AZD1402 compared to placebo on airway inflammation in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA.

iii) To investigate the PK profile and immunogenicity of AZD1402, and associated effects on safety.

iv) To evaluate the safety and tolerability of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA.

2.2.3 Exploratory Objectives

The exploratory objectives in Part 2 are:

i) CCI

ii) CCI

iii) CCI

iv) CCI

Note that, the exploratory objectives ii), iii), and iv) described above will not be presented as part of the final CSR, therefore, they are not part of this SAP.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a 2-part Phase IIa, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy and safety of AZD1402 administered via DPI, CCI for 4 weeks in adults with asthma on medium-to-highdose ICS.

3.1.1 Part 1

Part 1 of the study will be randomised, double-blind, placebo-controlled, and conducted in parallel for the 2 CCI dose levels (Part 1a) followed by an unblinded safety review and escalation to the CCI dose (Part 1b) dependent on the outcome of the safety review. Part 1a will consist of 30 participants who will be randomised 1:1:1 to receive 1 of the 2 CCI AZD1402 DPI doses (1 or CCI mg) or placebo in parallel. Part 1b will consist of 15 participants who will be randomised 2:1 to receive the CCI AZD1402 DPI dose (CCI mg) or placebo. Due to logistical reasons, the randomisation in Part 1 will be stratified by site in Australia and Germany.

The target population is adults with asthma (age 18 to 75, inclusive) who are adequately controlled on a stable medium dose ICS-LABA (and additional rescue medication as needed), Asthma Control Questionnaire-6 (ACQ-6) score $\leqslant$ 1.0, and pre-bronchodilator forced expiratory volume in 1 second (FEV_1) $\geqslant$ 70%, and with no exacerbation requiring systemic treatment or hospitalisation/emergency department visit for asthma during the 12 months prior to study start.

At Visit 3, following the 4-week Run-in Period, participants who remain controlled on a stable dose of ICS-LABA, and fulfil the entry criterion of FEV_1 $\geqslant$ 70% and have an ACQ-6 score of $\leqslant$ 1.0, will be randomised as follows:

<u>Part 1a Lead-in Cohort</u>

- AZD1402 inhalation CCI mg CCI

- AZD1402 inhalation [redacted] mg [redacted]
- Placebo inhalation [redacted]

Part 1b Lead-in Cohort

- AZD1402 inhalation [redacted] mg [redacted]
- Placebo inhalation [redacted]

Following randomisation to the 4 weeks of dosing, participants will remain at the clinic for a mandatory residential period of at least 2 weeks followed by 3 outpatient visits (Day 16, 20, and 24).

The participants are re-admitted to the clinic on Day 28 and discharged the next day (Day 29) followed by 2 outpatient visits (Day 30 and 32). Additionally, following the minimum 2-week residential period, participants may remain overnight in the clinic any time during Week 3 and Week 4 for any reason.

Part 1 will contain a total of 11 visits, and at Visit 7 participants will complete the Treatment Period. Two outpatient visits for safety and PK (Visit 8 and 9) are scheduled 1 and 3 days after discharge from the clinic. A follow-up (Visit 10) will occur 1 to 2 weeks following Visit 7, and a second and final follow-up (Visit 11), will occur 4 weeks after Visit 7.

3.1.2 Part 2

Part 2 will be randomised, double-blind, placebo-controlled and will include approximately 165 participants to evaluate 2 inhaled dose levels ([redacted] mg and [redacted] mg) of AZD1402 against placebo. Approximately 5 participants will be randomized to [redacted] mg and 80 participants will be randomized to [redacted] mg and placebo, respectively. The number of subjects enrolled in the [redacted] mg dose will depend on the enrolment rate and the randomisation ratio will change during the study. Patients will be randomised 2:1 (active to placebo) whilst the [redacted] mg arm is ongoing. Once the [redacted] mg has stopped recruiting and randomisation continues in the [redacted] mg and placebo arms, the randomisation ratio will be 1:1 (active to placebo).

Part 2, will be started after the unblinded safety review for Part 1a

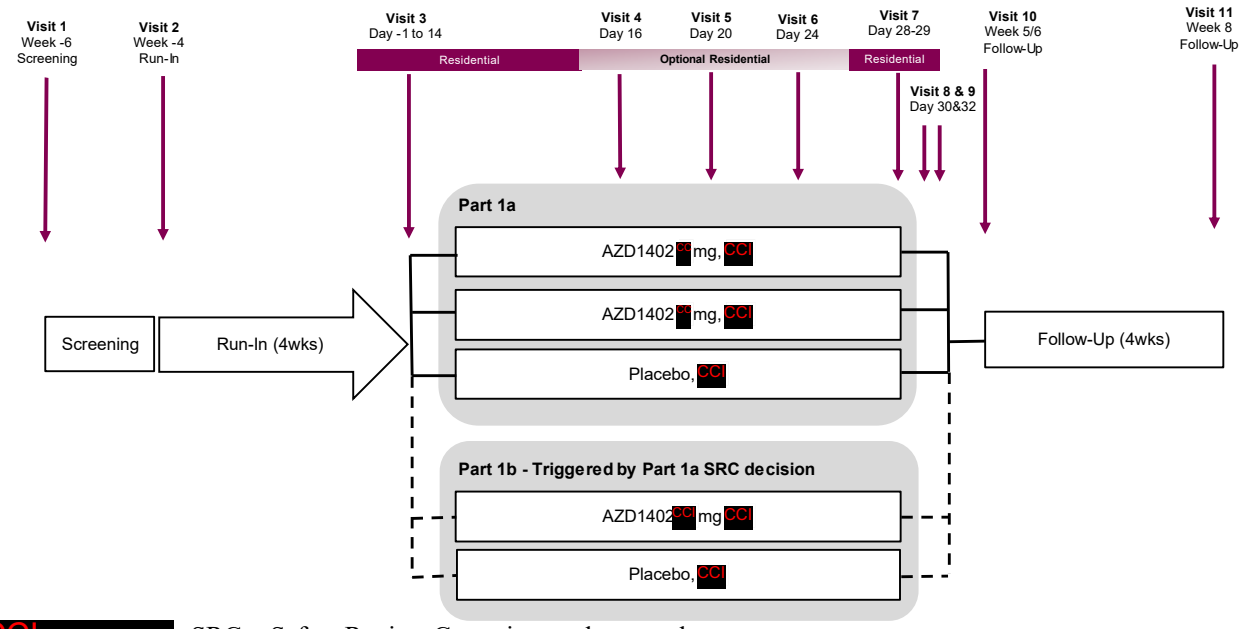
Part 2 will include:

- AZD1402 inhalation [redacted] mg [redacted]
- AZD1402 inhalation [redacted] mg [redacted]
- Placebo inhalation [redacted]

Part 2 will contain a total of 9 visits, and at Visit 7 participants will complete the Treatment Period. A follow-up (Visit 8) will occur approximately 1 to 2 weeks following Visit 7, and a second and final follow-up (Visit 9), will occur approximately 4 weeks after the end of treatment.

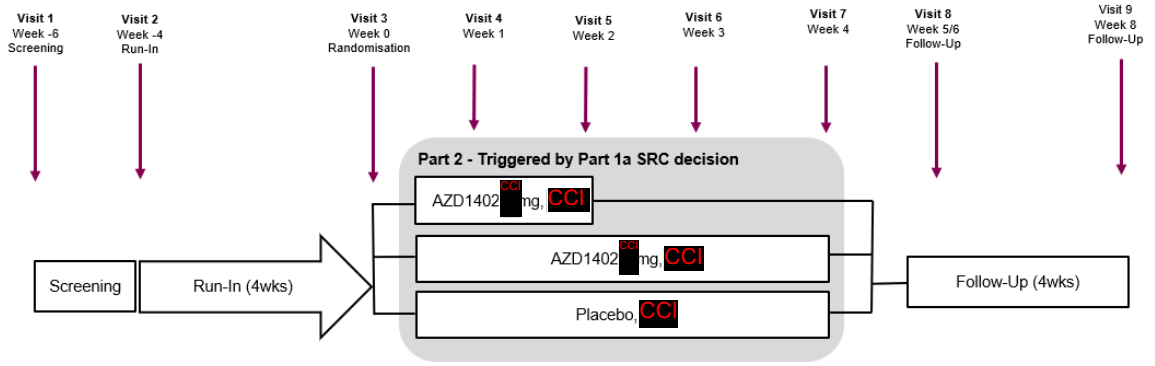
The entire study period for each participant in both Parts 1 and 2, is approximately 3.5 months; a 2-week Screening Period, a 4-week Run-in Period, 4 weeks of Treatment Period, and 4 weeks of Follow-up Period.

Figure 1 Study Design Part 1



CCI ; SRC = Safety Review Committee; wks = weeks.
Participants may also be required to attend a Visit up to 2 years after randomisation for a follow-up ADA sample.

Figure 2 Study Design Part 2



CCI SRC = Safety review committee

The Schedule of Assessments (SoA) for the Part 1 and Part 2 are provided in Table 2 and Table 3of Appendix 5.1. Further details regarding the study design are provided in Section 4 of the CSP.

A Safety Review Committee (SRC) will review unblinded safety data following completion of Part 1a before progressing to Part 1b and Part 2 and following completion of Part 1b treatment period.

A Data Safety Monitoring Board (DSMB) will oversee Part 2 of the study and review the unblinded interim outputs. Details of the composition of the DSMB, frequency of meetings and remit can be found in the DSMB Charter.

A separate review committee of AstraZeneca representatives will review the unblinded interim outputs for the interim analysis if performed.

3.2 Endpoints and Associated Variables

3.2.1 Efficacy Endpoints and Associated Variables (Part 2)

The primary efficacy variable to assess the primary objective for the Part 2 is the change from baseline in pre-bronchodilator FEV_1 at Week 4.

The secondary efficacy endpoints to investigate the efficacy of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA are:

- Change from baseline in pre-bronchodilator FEV_1 average over the 4-week Treatment Period (Visit 3 to Visit 7).
- Change from baseline in ACQ-6 at Week 4 and average over the Treatment Period (Visit 3 to Visit 7).
- Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 4 (Visit 7).
- Change from baseline in average morning peak expiratory flow (PEF) over the Treatment Period (Visit 3 to Visit 7).
- Change from baseline in average evening PEF over the Treatment Period (Visit 3 to Visit 7).
- Change from baseline in daily average asthma symptom score (AM/PM) over the Treatment Period (Visit 3 to Visit 7).

The secondary efficacy variable to investigate the effect of AZD1402 compared to placebo on airway inflammation in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA, is the change from baseline in fractional exhaled nitric oxide (in-clinic FeNO) at Week 4 (Visit 7) and average over the Treatment Period (Visit 3 to Visit 7).

3.2.1.1 Peak Expiratory Flow

Peak expiratory flow will be measured by the participant at-home after completing morning and evening e-Diary using a peak flow metre during the Run-in, Treatment Period, and Follow-up Period. Participants will be provided with a device at Visit 2 and receive training on PEF monitoring at that time. The PEF measurement must be done immediately upon waking up, after the participant has cleared out mucus CCI [redacted] and any rescue medication. The evening measurement should be done CCI [redacted]. The measurements should be made while standing and the best of 3 attempts recorded/reported.

3.2.1.2 Patient Reported Outcomes

Participants will be asked to complete the Patient Reported Outcomes (PRO) questionnaires on their e-Diary device supplied to the site according to the SoA (Table 2 and Table 3). During the study, all participants will be required to complete the e-Diary twice daily during the Run-in, Treatment, and Follow-up Period.

3.2.1.2.1 Asthma Control Questionnaire-6

The ACQ-6 was developed to measure asthma control and will be administered to participants as indicated in the SoA, Appendix 5.1. In the ACQ-6, participants will be asked to recall how their asthma has been during the previous week by responding to one bronchodilation use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and scores > 1.5 indicate not well-controlled asthma. Individual changes of at least 0.5 are considered clinically meaningful. More details on the ACQ-6 are included in Appendix H of the CSP.

3.2.1.3 Spirometry

Spirometry measurements (in-clinic spirometry), FEV_1 (L) and forced vital capacity (FVC; L), will be performed at the timepoints outlined in the SoA, (Table 2 and Table 3). For all participants, spirometry testing must be initiated between 6:00 AM and 11:00 AM during the screening or re-screening period. If possible, all post-randomisation morning spirometry assessments should be performed within ± 1.5 hours of the time that the randomisation spirometry was performed. For example, if the randomisation spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM. The evening spirometry should also be performed within a 2 hours window relative to the evening assessment time point.

3.2.1.4 Fractional Exhaled Nitric Oxide

FeNO test and FeNO at-home assessments will be measured at the timepoints outlined in the SoA, (Table 2 and Table 3). On days when spirometry and FeNO are to be performed on the same day,

measurement should always be carried out prior to spirometry assessments.

3.2.1.5 Asthma Symptom Score

Severity scores for asthma symptoms will be recorded BID in the morning and evening and documented in the e-Diary during the Run-in, Treatment Period, and Follow-up Period. Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment. Night-time is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

Asthma symptom scores during night-time and daytime will be assessed by the participant each morning and evening according to the following scoring system:

0: You have no asthma symptoms.

1: You are aware of your asthma symptoms, but you can easily tolerate the symptoms.

2: Your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep).

3: You are unable to do your normal activities (or to sleep) because of your asthma.

3.2.2 Safety Endpoints and Associated Variables

Vital signs, laboratory abnormalities, and electrocardiograms (ECGs) collected at the Screening visit and associated with pre-existing medical conditions (for example hypertriglyceridemia, elevated

glucose, increased body mass index [BMI]) may be reported as medical history if applicable and should not be reported as adverse events (AEs).

3.2.2.1 Adverse Events/Serious Adverse Events

Adverse events, including serious AEs (SAEs) will be collected from the time the subject signs the Informed Consent Form (ICF), throughout the Run-in, Treatment Period, and Follow-up Period for any study phase. All AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

The following variables will be collected for each AE:

- AE diagnosis/description (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to investigational product (IP)
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

Additional variables will be collected for all SAEs including treatment given for the event:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to (ie, seriousness criteria)
- Probable cause of death
- Date of death
- Required in-patient hospitalisation or prolongation of existing hospitalisation
- Date of hospitalisation/discharge
- Autopsy performed
- SAE caused by other medication or study procedure

The following intensity ratings will be used:

1. mild (awareness of sign or symptom, but easily tolerated)
2. moderate (discomfort sufficient to cause interference with normal activities)
3. severe (incapacitating, with inability to perform normal activities)

Some AEs are considered of special interest (AESI).

Additionally, C-reactive protein (CRP) ≥ 10 mg/L should be used to support the evaluation and identification of the potential cause of an AESI and to guide further dosing.

3.2.2.2 Laboratory Assessments

Laboratory assessments (haematology, coagulation, clinical chemistry, urinalysis, QuantiFERON® Tuberculosis [TB] Gold test, assessments of CRP, severe acute respiratory syndrome coronavirus 2

[SARS-CoV-2] serology, SARS-CoV-2 polymerase chain reaction [PCR] and urine pregnancy test) will be performed at the timepoints specified in the SoA, Section 5.1.

Clinical chemistry, haematology, coagulation, and urinalyses will be analysed centrally.

Assessment of CRP, SARS-CoV-2 PCR, urine cotinine, and urine pregnancy tests will be analysed locally/on site.

Blood samples will be collected for immuno-biomarker testing to assess the safety of AZD1402 and per the timepoints mentioned in the SoA (Table 2 and Table 3) for analysis of immuno-biomarkers including, but not limited to:

Cytokines, local CRP, high sensitivity (hs)-CRP, and immunoglobulins including immunoglobulin E (IgE).

The following parameters will be assessed:

Table 1 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin	SARS-CoV-2 PCR
B-Haematocrit	S/P-Creatinine
B-Erythrocytes	eGFR
B-Reticulocytes (abs, %)	S/P-Bilirubin, total
B-Platelet count	S/P-Alkaline phosphatase
B-Mean corpuscular volume	S/P-Aspartate transaminase
B-Mean corpuscular haemoglobin	S/P-Alanine transaminase
B-Mean corpuscular haemoglobin concentration	S/P-Albumin
B-Red cell distribution width	S/P-Glucose (fasting and non-fasting)
B-Red blood cell morphology	S/P-Cholesterol***
B-Leucocyte count	S/P-Triglycerides***
B-Leukocyte differential count	S/P-C-reactive protein
B-Neutrophils (abs, %)	S/P-Potassium
B-Lymphocytes (abs, %)	S/P-Calcium, total
B-Eosinophils (abs, %)	S/P-Sodium
B-Monocytes (abs, %)	S/P-Creatine kinase
B-Basophils (abs, %)	S/P-high sensitivity C-reactive protein
Urinalysis (dipstick)*	S/P-Direct Bilirubin
U-Haemoglobin/Erythrocytes/Blood	S/P-Indirect Bilirubin (calculation)
U-Protein/Albumin	S/P-Gamma glutamyl transferase
U-Glucose	S/P-Lactate dehydrogenase
U-drug screen**	S/P-Urea nitrogen
U-Specific gravity	S/P-Uric acid
U-pH	S/P-Phosphorus
U-Protein	S/P-Total protein
U-Ketones	S/P-Globulin (calculation)
U-Bilirubin	S/P-Bicarbonate
U-Urobilinogen	S/P-Chloride

Table 1 Laboratory Safety Variables

U-Nitrite	S/P-Magnesium
U-Leukocyte Esterase	**Coagulation**
Others	International normalised ratio
Hepatitis B Core Total	Activated partial thromboplastin time
Anti Hep B Surface AG2 Qual	Prothrombin time
Hepatitis B - Qual	**Reproductive hormones (Females only)**
Hepatitis B - PCR****	U-human chorionic gonadotropin hormone
Hepatitis C - Virus Antibody	S-human chorionic gonadotropin hormone
Hepatitis C - PCR****	S-Follicle stimulating hormone
HIV 1/2 Ag/Ab Screen	**Safety-Immuno-biomarkers**
HIV-1 Ab Supplemental, Geenius	C-reactive protein
HIV-2 Ab Supplemental, Geenius	Immunoglobulins
HIV Ab Interpretation, Geenius	Cytokines*****
HIV Confirmation	Tryptase
QuantiFERON-TB Gold test	
SARS-CoV-2-serology	
SARS-CoV-2 PCR	

*If clinically relevant abnormalities are detected (positive result in dipstick), the urine sample will be sent to the central laboratory for analysis of the sediment.
**Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates
***Cholesterol and triglycerides will be measured at Screening, baseline (Day 1 pre-dose), and Day 28
**** Participants with positive anti HBsAg test, negative HBsAg and negative hepatitis B core total at Screening may be included into the study if they have a positive vaccination history. Participants where the interpretation of the hepatitis B panel results is inconclusive, may be included following the confirmation of a negative PCR test. Assessments will preferably be done centrally but may be done locally
***** Cytokines may include, but are not limited to IFNγ, IL-10, IL-12p70, IL-13, IL-1b, IL-2, IL-4,IL-6, IL-8,TNFα
Abbreviations: eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TB = tuberculosis

3.2.2.3 Vital Signs

The vital signs assessments will be performed at the timepoints specified in the SoA, Section 5.1.

The following variables will be collected:

- Systolic blood pressure (SBP) (mmHg)
- Diastolic BP (DBP) (mmHg)
- Pulse rate (beats per minute [bpm])
- Oral or tympanic body temperature (°C)
- Respiratory rate (breaths per minute)

The vital signs to be assessed (prior to study intervention) are blood pressure (BP; in mmHg) and pulse rate (in bpm), temperature (oral or tympanic, in °C), and respiratory rate measurements (breaths per minute).

Systolic BP and DBP will be measured after at least 5 minutes resting, and before taking any blood sample and conducting any spirometry.

Measurements will be carried out with the participant in a seated position and preferably always on the same arm.

If there is any suspicion of an unreliable measurement, BP will be measured again. The value obtained on the second measurement will be considered as definitive and will be recorded on the electronic Case Report Form (eCRF).

3.2.2.4 12-lead Safety Electrocardiogram

At the timepoints specified in the SoA, Section 5.1, 12-lead ECGs will be obtained after the subject rested in the supine position for at least 5 minutes and should be measured before any blood sampling and spirometry assessments are completed. The ECG machine used should automatically calculate the heart rate and measures RR, PR, QRS, QT, and QTcF intervals.

The following ECG parameters will be determined:

- Heart rate.
- RR-interval: Duration in milliseconds between 2 R peaks of 2 consecutive QRS complexes.
- PR-interval: Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R).
- QRS interval: Duration in milliseconds of the QRS complex.
- QT interval: Duration in milliseconds from the beginning of Q wave to the end of the T-wave.
- QTcB-interval: QT interval corrected using Bazett's formula (QT[msec]/ RR[sec]1/2).
- QTcF interval: QT interval corrected using Fridericia's formula (QT[msec]/RR[sec]1/3).

The investigator will judge the overall interpretation as normal, abnormal, or borderline and/or clinically significant.

3.2.2.5 Physical Examinations

The full and brief physical examinations will be performed at the timepoints outlined in the SoA, Section 5.1.

The results of the physical examination at screening will be documented in medical history for each subject.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

Full

The complete physical examinations will include an assessment of the 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.

Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular, and respiratory system.

3.2.2.6 In-clinic and At-home Spirometry

For details on the in-clinic spirometry, refer to Section 3.2.1.3.

During the study period, participants will be required to monitor lung function at-home BID using an at-home spirometry device. Participants should follow the relevant medication and other restrictions beforehand.

3.2.2.7 Fractional Exhaled Nitric Oxide

For details on this assessment, refer to Section 3.2.1.4

3.2.3 Pharmacokinetic Endpoints and Associated Variables

Blood samples for PK assessments will be collected from all the participants at timepoints mentioned in the SoA (Table 2 and Table 3).

Intense sampling will be performed in Part 2 of the study in a subset of approximately 20 participants per treatment arm at timepoints mentioned in the SoA (Table 2 and Table 3).. The participants in these subsets may be asked to stay in the clinic overnight for logistical reasons depending on the sampling timepoints.

Pharmacokinetic analysis for AZD1402 from intense sampling profiles will be performed by bioanalytical test sites operated on behalf of AstraZeneca Research and Development.

Where data allow, the following PK parameters for AZD1402 will be derived from serum concentrations:

Cmax	Maximum observed serum (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
Ctrough	Observed lowest drug concentration reached before the next dose is administered (pre-dose)
λz	Terminal rate constant, estimated by log linear least squares regression of the terminal part of the concentration-time curve
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
AUClast	Area under the serum concentration-curve from zero to the last quantifiable concentration
AUCτ	Area under serum concentration-time curve in the dosing interval τ
CL/F	Apparent total body clearance of drug from serum after extravascular administration
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)
Dose normalised AUCτ	Area under the serum concentration-time curve in the dosing interval τ divided by the dose administered in mg
Dose normalised Cmax	Maximum observed serum (peak) drug concentration divided by the dose delivered in mg
Dose normalised AUClast	Area under the serum concentration-curve from zero to the last quantifiable concentration divided by the dose delivered in mg
tlast	Time of last observed (quantifiable) serum concentration
Rac AUC	Accumulation ratio for AUCτ
Rac Cmax	Accumulation ratio for Cmax

The following diagnostic parameters for PK analysis will be provided:

λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
Rsq	Statistical measure of fit for the regression used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
λz span ratio	Time period over which λz was determined as a ration of t½λz

Additional PK parameters may be determined where appropriate.

3.2.4 Immunogenicity Endpoints and Associated Variables

Blood samples for determination of ADA in serum will be collected as specified at timepoints mentioned in the SoA (Table 2 and Table 3).

Immunogenicity parameters are:

- ADA
- Immunogenicity titre

These parameters are tested in an external laboratory. A validated screening assay will be used to determine ADA positive samples. Any positive samples will be tested in a confirmatory assay whereby the specificity of the ADA response will be confirmed as either positive or negative with respect to AZD1402. Titre evaluations are performed on samples that are confirmed positive for ADA.

Anti-drug antibodies will be defined as positive when titre measurements reported as ≥ 10 (minimum required dilution).

All these parameters are assigned to the analysis visits and to the analysis phases as described in Figure 1 and Figure 2 of Section 3.1.2. Measurements with missing or partial missing dates are not assigned to any analysis visit.

The study day of ADA measurement is calculated as the date of the ADA sample collection – the date of first IP +1 for ADA sample collected on or after the day of first IP and as the date of the ADA sample collection – the date of first IP for ADA sample collected before the day of first IP.

3.2.5 Exploratory Endpoints and Associated Variables

Part 1:

The exploratory endpoints for Part 1 are:

- Change from baseline in FeNO at Day 28 and average over the Treatment Period.
- CCI [redacted]
- Change from baseline average in cough VAS over the Treatment Period.

For details on these assessments except cough VAS, refer to Section 3.1.2.

Part 2:

The exploratory endpoints for Part 2 are:

- Change from baseline in FeNO (in-clinic).

3.2.5.1 Cough VAS

In Part 1 participants will be asked to complete a cough severity VAS (100 mm linear scale marked with a horizontal line by the participant, with 0 mm representing "no cough" and 100 mm representing "worst cough") measuring subjective assessment by the participant for the prior 24 hours for severity of cough symptoms. More details on the Cough VAS are included in the Appendix H of CSP.

3.2.5.2 CCI

CCI

3.2.5.3 CCI

CCI

3.2.5.4 CCI

CCI

3.2.5.5 Fractional Exhaled Nitric Oxide

For details on this assessment, refer to Section 3.2.1.4.

3.2.5.6 Cough VAS

For details on this assessment, refer to Section 3.2.1.2.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

'Baseline' (unless stated otherwise) is defined as the last available pre-treatment assessment. 'End of Study' is defined as the last available post-treatment assessment. 'Treatment Day' will be calculated

relative to the date of randomisation, ie, Treatment Day = Assessment Date - Randomisation Date + 1.

All variables, if not otherwise specified, will be summarised by each Part (Part 1 and Part 2) and study treatment group (dose level of AZD1402 or placebo) and AZD1402 overall (when required), using descriptive statistics, tables and/or figures, as applicable.

Continuous data will in general be summarised in terms of the mean, standard deviation (SD), median, minimum, maximum, and number of observations. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile (Q3), median, lower quartile (Q1), minimum and number of observations.

The same level of precision should be used for means, SD, SE, and CIs. The minimum and maximum values would normally be reported to the same number of decimal places as the individual values, unless a decision has been made to report the summary statistics to a lesser number of decimal places than the original data. Medians may be presented to 1 more decimal place than the recorded values to account for ties.

In general, the maximum number of decimal places reported shall be 4 for any summary statistic. These summaries will be provided by timepoint of assessment as appropriate. If at a given timepoint, $n < 3$, then only n, minimum and maximum will be presented. If $n = 3$, then only n, mean, median, minimum, and maximum will be presented. The other descriptive statistics will be left blank.

A missing category shall be included only for categorical variables where no data is available. The missing category will be omitted if there were no missing values for that variable. Categorical data will be summarised in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to 1 decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarised using shift tables where appropriate.

All confidence intervals (CIs) will be 2-sided 95% CIs, unless stated otherwise, and presented to one more decimal place than the raw data recorded in the database. If a model is used to estimate the treatment difference, the corresponding CI according to the model will be presented. Otherwise, the unadjusted CI will be used. Nominal p-values may also be presented. Care should be taken when interpreting CIs and p-values since no correction for multiple testing is done for the endpoints.

P-values greater than or equal to 0.001, in general, will be presented to 3 decimal places. P-values less than 0.001 will be presented as "<0.001".

Descriptive statistics for calculated PK parameters and FeNO will include: n, mean, SD, geometric mean, geometric coefficient of variation (GeoCV%), median, minimum and maximum values.

The GeoCV% will be calculated as $SQRT(e^{s^2}-1)*100$ where s is the SD of the log-transformed values.

Daylight saving dates will be considered in the calculation of the absolute scheduled and actual times and in the duration when this is based on times. Therefore, if any daylight saving change occurs during the study development, this will impact the description of the blood sample collections, the calculation of the PK parameters and any AE duration in case the time is included in the calculation of the duration.

All other requirements and specifications for programming and presentation of TFLs will be specified in the TFL shells document.

The following rules will be applied for any repeated safety assessments:

- For repeated assessments at any timepoint before first IP administration (including screening values and baseline): the latest assessment obtained per timepoint will be used in the calculation of descriptive statistics.
- For repeated assessments at any timepoint after first IP (including Follow-up visit): the first (non-missing) value after dosing will be used in the calculation descriptive statistics.

The AM and PM assessments will be combined into a daily assessment according to the following formula:

Let assessment (Day i) = (PM assessment (Day i) + AM assessment Day (i+1)) / 2

4.3 Software

All report outputs will be produced using SAS® version 9.4 in a secure and validated environment.

PK parameters will be calculated using Phoenix® WinNonlin (WNL) version 8.1 or a later version in a secure and validated environment.

All TFLs will be presented in individual files (.rtf or.docx) and also in one portable document format (PDF and.docx) book-marked document containing all Tables and Figures (14.x outputs) combined and distinct PDF book-marked files for each of the 16.2.x subsections, ie, one for all 16.2.1.x outputs, one for all 16.2.2.x outputs, etc.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided for each study part, from screening to study completion.

Subject disposition will be summarised for screening failures (in the screening phase), subject discontinuation during Run-in phase, randomised subjects separately for each study part. Screening failures data will be summarised based on the subjects enrolled in the study.

The following information will be provided:

- Number of subjects screened.
- Number of screening failures including the reason of failing.

Disposition summaries of randomised subjects will be presented for each study Part by treatment group (each dose level of AZD1402, placebo, and pooled AZD1402), and overall and include the following information:

- Number of subjects randomised.
- Number of subjects randomised, not treated, including the reason.
- Number and percentage of subjects who started treatment.
- Number and percentage of subjects who completed treatment.

- Number and percentage of subjects who discontinued treatment, including the reason.
- Number and percentage of subjects who completed study part.
- Number and percentage of subjects who withdrawn from study part, including the reason.
- Number and percentage of subjects who discontinued treatment due to global/country situation
- Number and percentage of subjects who withdraw due to global/country situation.

Percentage will be based on number of subjects started the treatment.

A disposition figure will be also presented for each treatment and study part.

The global country situation study disruption will be summarised.

A subject who completed the study Part is defined as a subject who completed all scheduled visits including the Follow-up visit.

A subject who completed the treatment is defined as a subject who completed the treatment period.

Subjects' discontinuations will be listed including the date of study discontinuation, treatment duration exposure (in days) as well as reason for discontinuation for each study part.

Subject affected by the global/country situation will also be presented in listings.

The number of subjects recruited per country/site will be also summarised by analysis population and treatment group.

4.4.2 Protocol Deviations

Important protocol deviations (IPD) are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of IPD on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by IPD.

This evaluation will be performed on a Blind Data Review Meeting (BDRM) shortly before database lock/unblinding. Results and population assignments will be summarised in a BDRM report which will be signed off by all relevant scientific experts.

Important protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification. The IPD will be summarised for each study part by treatment group (each dose level of AZD1402, placebo, and pooled AZD1402), and overall.

The IPD include the following:

- Inclusion/exclusion criteria deviations.
- Treatment deviations.
- Visit out of window.
- Subjects receiving prohibited concomitant medications.
- Procedures not performed or out of window.

By-participant listings of IPD will be provided.

4.5 Analysis Sets

A summary of the number and percentage of subjects included and excluded from each analysis population will be presented by treatment group and overall, for each part of the study.

A by subject listing of analysis set details should be provided. This listing should be presented by treatment group and should include subject identifier, exclusion flag for each population, and reason for exclusion from each analysis set. All subjects randomised should appear in this listing.

A BDRM will be held before opening randomisation codes in order to assign the subjects to the different analysis populations according to the specified definitions. The precise reasons for excluding subjects from the study populations will be fully defined and documented in the BDRM Report.

4.5.1 Safety Set

The Safety set (SS) will include all participants who are randomised and received any study intervention.

Participants are evaluated according to the actual treatment they received.

If a participant received a different treatment dose than randomised throughout the study, they will be analysed according to treated dose, not the randomised dose. If a participant received study intervention from the wrong kit for only part of the treatment duration, they will be analysed according to their randomised dose.

The SS will be used for all safety analyses.

4.5.2 Full Analysis set

The Full analysis set (FAS) will include all participants who are randomised and received any study intervention.

Participants are evaluated according to the treatment assigned at randomisation.

The FAS will be used for all analyses of demographic baseline characteristics and efficacy data.

4.5.3 Pharmacokinetic Set

The Pharmacokinetic set (PKS) set will include all participants in the SS who have detectable PK data, and with no major protocol deviations considered to impact on the analysis of PK data.
The exclusion of any participants or timepoints from the calculation of the PK parameters or statistical analysis will be documented by the PK scientist including the reason(s) for exclusion prior to the unblinding of the study. The available concentration data and PK parameter data for any participants excluded from the PK analysis set will be listed only and presented in the individual figures of concentration-time plots.

The PK analysis set will be used for all PK analyses. For the SRCs at completion of Part 1a before progressing to Part 1b/2a and from Part 1b before progressing to Part 2b the protocol deviations for the PK set will not be evaluated.

4.5.4 Immunogenicity Set

The Immunogenicity set (IS) will include all participants in the SS with at least 1 post-treatment ADA result (positive or negative), with exception for any analysis of relationship of ADA with PK where will instead include all participants in the PK set.

The immunogenicity analysis set will be used for all ADA analyses.

All the immunogenicity parameters and listings will be based on the IS and presented for each treatment group.

4.6 Demographics and Baseline Characteristics

Analyses of demographic and baseline characteristics will be performed on the FAS.

Demographic characteristics to be assessed are age (years), sex, race, ethnic group and country. Age groups 18 to 64, 65 to 75 will also be presented (for EudraCT reporting).

For demography, height/weight baseline is defined as the assessment on screening

Participant baseline characteristics to be assessed are height (cm), weight (kg), BMI (kg/m^2), CRP (mg/L) and Eosinophils count (10^9 /L), and smoking history.

Asthma characteristics at baseline will include: time since asthma diagnosis, time since last exacerbation, number of exacerbations and most recent exacerbation type in the 12-month period preceding the subject enrolment in the study.

- Time since asthma diagnosis (years) is calculated as follows:
  (Asthma diagnosis date-Screening date/Re-screening date) /365.25
- Time since last exacerbation (days) is calculated as follows:
  (Last exacerbation date- Screening date/Re-screening date) + 1

For missing day and/or month the following strategy will be followed:

- Initial asthma diagnosis date/last exacerbation date with valid year and month but missing day:

Such a date will be assumed at the 15th of the month in the Year.

- Initial asthma diagnosis date with valid year but missing month and day:

Such a date will be assumed at the 15th of June in the Year,

Baseline lung function data to be assessed for Part 1 include:

- In-clinic pre-bronchodilator FEV_1 and FVC in absolute value (L) and percent of predicted values (% PN).
- In-clinic pre-bronchodilator ratio FEV_1/FVC (%).
- Home assessment pre-bronchodilator spirometry absolute values of FEV_1 (L).
- In-clinic FeNO (part per billion [ppb]) (geometric mean and geometric coefficient of variation [GeoCV (%)] will be presented instead of mean and SD for this variable).
- FeNO at home assessment (ppb) (geometric mean and GeoCV [%] will be presented instead of mean and SD for this variable).

Lung function and reversibility data at screening to be assessed for Part 2 include:

- In-clinic pre-bronchodilator FEV_1 and FVC in absolute value (L) and percent of predicted values (% PN).
- In-clinic pre-bronchodilator ratio FEV_1/FVC (%).
- Home assessment pre-bronchodilator spirometry absolute values of FEV_1 (L).
- In-clinic post-bronchodilator FEV_1 and FVC in absolute value (L) and percent of predicted values (% PN).
- In-clinic post-bronchodilator ratio FEV_1/FVC (%).

Baseline lung function data to be assessed for Part 2 include:

- In-clinic FEV_1 in absolute value (L)
- In-clinic FeNO (part per billion [ppb]) (geometric mean and geometric coefficient of variation [GeoCV (%)] will be presented instead of mean and SD for this variable).

Baseline diary data to be assessed for CCI Part 2 include:

- ACQ-6 score

Baseline diary data to be assessed for Part 1 include:

- Cough VAS (mm)

Baseline diary data to be assessed for Part 2 include:

- Morning PEF (L/min).
- Evening PEF (L/min).
- Daily asthma symptom score.

The daily values of rescue medication use and of asthma symptom scores are calculated as the mean of the evening measurement for day n and the morning measurement for day n + 1.

Additional baseline assessments to be assessed for Part 1 and Part 2 include:

- Eosinophils count (10^9/L).
- hsCRP (mg/L).

Additional baseline assessments to be assessed for Part 2 include:

- Eosinophils count group (cells/µL): < 300, ≥ 300.

The baseline assessments detailed above will be summarised by treatment group (each dose level of AZD1402, placebo, and pooled AZD1402) and overall.

By-participant listings of demographics, participants characteristics, asthma history will be provided for the randomised subjects. For weight, height and BMI, and asthma exacerbation the listings will be presented for the safety set. All listings will be presented for each study Part.

4.6.1 Baseline, Change from Baseline and Percentage Change from Baseline Definitions

In general, the baseline which will be used in calculation of change from baseline will be the last value obtained before first study intervention.

Exceptions to the general definition of baseline (for calculation of change from baseline) are the following:

- In-clinic FeNO test: baseline is defined as the mean of measurements at Day -1 and at Day 1 morning pre-dose at Visit 3 in Part 1 and as Day 1 morning pre-dose at Visit 3 in Part 2.
- FeNO at home assessments: baseline is defined as the mean of all available measurements during the 7 days period prior to Day 1 in Part 1.
- In-clinic pre-bronchodilator FEV_1, FVC and FEV_1/FVC in absolute values and in percent of predicted values: baseline for Part 1 is the mean of measurements at Day -1 and at Day 1 morning pre-dose at Visit 3; for Part 2 is the pre-bronchodilator assessment at Visit 1.
- In-clinic FEV_1 is the mean of Day -1 and Day 1 morning pre-dose at Visit 3 for Part 1 and is the mean of measurements at Day 1 pre-dose timepoints (15 and 45 minutes pre-dose) for Part 2.
- In-clinic post-bronchodilator FEV_1, FVC and FEV_1/FVC in absolute values and in percent of predicted values: baseline is the measurement at Visit 1 (1 measurement) within performed 15 to 30 minutes after inhalation of 400 µg of salbutamol.
- FEV_1 home spirometry: baseline is defined as the mean of all available measurements during the 7 days period prior to Day 1 in both Part 1 and Part 2. i.e. The baseline for the morning assessments will be: the mean of all available morning measurements in the 7 days period prior to Day 1. Same approach will be used for the baseline for the evening assessments.
- e-Diary variables (cough VAS, CCI [redacted], evening PEF, daily asthma symptom score): baseline is average over measurements on the 7 days prior to randomisation. For the morning assessments of PEF, daily use of rescue medication and asthma symptoms the baseline is average over morning assessments from Day -6 to Day -1 and the Day 1 pre-dose assessment.

For e-Diary any study day will be derived relative to randomisation.

In case of missing values among the measurements defining the baseline of the e-Diary variables, the baseline will be defined as the mean of all available measurements in the 7 days period. In all other cases of missing values in measurements defining a baseline, the baseline value will be defined as the last non-missing value prior to Day 1.

Change from baseline will be defined as the value post-dosing minus the baseline defined, for each timepoint.

Percent change from baseline will be calculated as:

- Percent change from baseline = ((visit value – baseline value)/baseline value) ×100%

The average change from baseline over the treatment period will be calculated from the subjects' average measurements of all assessments performed while subjects are on-treatment, minus the baseline value.

If either a visit value or the baseline visit value is missing, the absolute change from baseline value and the percent change from baseline will also be set to missing.

4.7 Medical History and Concomitant Illnesses

Medical and surgical history (presented together) and concomitant illness will be listed by subject including treatment, description of the disease/procedure, MedDRA System Organ Class (SOC), MedDRA preferred term, start date and stop date (or ongoing if applicable) based on the FAS.

A summary of the number and percentage of subjects with any relevant medical history, surgical history and concomitant illness will be summarised based on the FAS for each study Part by each dose level of AZD1402, placebo and pooled AZD1402 and overall, by SOC and preferred term.

4.8 Prior and Concomitant Medications

Prior medication stopped prior to the first dose of IP (exclusive), as well as all concomitant medications taken during the conduct of the study will be described.

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO-DD), version March 2020 or later.

Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either prior only, both prior and concomitant, or concomitant only. Medications starting after the completion + 4 days/discontinuation of the treatment/will be listed but will not be classified or summarised.

Medications that started and stopped prior to the first dose of IP (exclusive) will be considered as prior medications. Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that starts after first dose of IP will be recorded as concomitant.

If a medication starts prior to the first dose of IP and continued on or and stops after first dose of IP then the medication will be classified as both prior and concomitant. Medications will be classified as concomitant only if they have a start date on or after first dose of IP and during the study conduct (including Follow-up Period).

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of the first dose of IP. Medications will be assumed to be concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to the first dose of IP. If there is clear evidence to suggest that the medication started prior to the first dose of IP, the medication will be assumed to be both prior and concomitant, unless there is clear evidence to suggest that the medication stopped prior to the first dose of IP. If there is clear evidence to suggest that the medication stopped prior to the first dose of IP, the medication will be assumed to be prior only.

Prior and concomitant medications will be listed by subject, treatment group, and study part and will include the following information: reported name of drug, medications or therapy, anatomical therapeutic chemical (ATC) and generic drug name, the route of administration, dose, frequency, study day of start of medication and duration, and indication.

A summary of prior medications received and concomitant medications, preferably by ATC level 4 category when possible or the highest ATC level when level 4 is not available and generic drug name, and by treatment part will be reported.

The duration will be calculated as:

- Duration (in hours) = end date/time – start date/time, in case date and time is available.
- Duration (in days) = (end date – start date) + 1, in case only date is provided.

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

For summary tables, multiple records for a subject in the same ATC level 4 category when possible or the highest ATC level when level 4 is not available and generic drug name will be counted only once.

4.9 Treatment Exposure/Compliance

4.9.1 Treatment Exposure

In the assessment of the treatment exposure, interruptions will be considered.

When there is no interruption treatment exposure duration (in days) will be calculated as follows:

Treatment exposure duration (in days) = min (date of last dose received, date of death, data of data cut-off) - date of first dose received) + 1.

When there is any interruption treatment exposure duration will be calculated as follows:

- for each interruption the duration of interruption will be calculated as follows:
  (date of first dose received after the interruption - date of first day of interruption).
- the treatment exposure duration (in days) will be calculated as follows:
  Treatment duration (in days) = (date of last dose received, date of death, data of data cut-off - date of first dose received) + 1 – (sum of interruptions).

Treatment duration of exposure (days) will be summarised per each Part by treatment for the SS, using descriptive statistics.

A by subject listing of drug administration data will be provided.

4.9.2 Treatment Compliance

Compliance will be assessed by checking the daily e-Diary and eCRF.

For all treatments, treatment compliance will be calculated as:

$$\text{Treatment compliance (\%)} = \frac{\text{Number of doses taken during treatment period}}{\text{Number of doses planned (28 days*) during treatment period}} \times 100.$$

*The number of doses planned is 55 since there is only 1 dose in the morning of Day 28.

Compliance is expected to be $\geqslant$ 80% during the Treatment Period.

4.10 Efficacy Evaluation

All the efficacy analysis will be based on FAS.

4.10.1 Analysis and Data Conventions

No statistical hypotheses will be tested in Part 1 (Lead-in Cohort) of this study. Part 2 (Main cohort) of this study aims to demonstrate that AZD1402 improves FEV_1 compared to placebo.

The null hypotheses for the primary analysis in Part 2 is that there is no difference in the change from baseline at Week 4 (Visit 7) in pre-bronchodilator in-clinic FEV_1 in AZD1402 treated participants compared to placebo-treated participants.

The following comparisons will be performed:

- AZD1402 inhalation CCI mg CCI versus placebo inhalation CCI.
- AZD1402 inhalation CCI mg CCI versus placebo inhalation CCI

4.10.2 No formal comparisons between the different AZD1402 doses will be conducted. Adjustments for Covariates

The primary efficacy analysis for Part 2 will be adjusted for the following baseline covariates:

1. Country (stratification variable)
2. Baseline FEV_1

4.10.3 Handling of Dropouts or Missing Data

With exception of some dates for the AEs calculation, missing data will not be imputed.

In case the end date of the treatment is known but the time is missing, then end time will be imputed with a time of 00:00.

The analysis based on mixed model for repeated measure (MMRM) will be performed using only the observed measurements without imputation of missing values.

4.10.4 Multiple Comparisons/Multiplicity

No adjustments for multiple testing will be performed.

4.11 Primary Efficacy Variable (Part 2)

The primary variable for the assessment of efficacy for Part 2 is the change from baseline pre-bronchodilator in-clinic FEV_1 at Week 4.

The change from baseline in pre-bronchodilator FEV_1 will be analysed using MMRM with treatment group, week (1 to 4), country, baseline FEV_1, and treatment-by-week interaction as fixed effects and with participant as random effect. In this model, Week 1 to Week 4 corresponds to Visit 4 to Visit 7.

The within participant correlation will be modelled using the unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate the degrees of freedom. The REML method will be applied.

If the estimating algorithms will not converge, the following steps will be taken to simplify the model until convergence is achieved:

1. As a first step, try in order these 3 covariance structures: Toeplitz, the first-order autoregressive, and compound symmetry. Stop as soon as convergence is achieved.

2. If step 1 does not work, the treatment-by-week interaction will be removed from the last model in step 1, ie, from the model with compound symmetry.
3. In case non-convergence persists, the analysis will be changed to use the analysis of covariance (ANCOVA) instead of mixed-effects model for repeated measures.

Each treatment effect and treatment comparisons (all active treatments to placebo) will be estimated by the Least Square means (LS means) and the difference in LS means at the corresponding week (Week 1, Week 2, Week 3, Week 4) on the treatment-by-week interaction, along with their standard errors (SE) and 95% CIs, and the p-value corresponding to the between-treatment group difference. A plot showing the LS mean change (+/- SE) from baseline in FEV_1 over time within each treatment group will be provided.

Missing values will not be imputed. In this analysis it is thus assumed that any missing FEV_1 values are missing at random.

A listing of the primary efficacy data will be provided based on the FAS.

4.12 Secondary Efficacy Variables (Part 2)

4.12.1 Forced Expiratory Volume in One Second

The analysis of change from baseline in pre-bronchodilator in-clinic FEV_1 average over the treatment period will be conducted as part of the analysis for the primary endpoint as described in Section 4.11. The overall treatment effect and treatment difference over the 4-week treatment period will be estimated by the LS means and the difference in LS means on the treatment factor, along with the SEs, and 95% CIs and the p-value corresponding to the between-treatment group difference.

4.12.2 Asthma Control Questionnaire-6

A summary by treatment group (different doses of AZD1402, pooled AZD1402 and placebo) in terms of absolute values at baseline and average over the treatment period, as well as change from baseline and its average over the treatment period, will be presented for ACQ-6. Information from ACQ-6 assessments will also be listed. The average over the treatment period will be calculated from the subjects' average measurements of all assessments performed while subjects are on-treatment. Also, the number and percentage of participants with a decrease in ACQ-6 score of ≥ 0.5 (responders) over the treatment period for each treatment group will be described.

4.12.3 PEF and Asthma Symptoms Score

A summary by treatment group (different doses of AZD1402, pooled AZD1402 and placebo) in terms of absolute values at baseline and average over the treatment period, as well as change from baseline and its average over the treatment period, will be presented for average morning PEF, average evening PEF and in daily average asthma symptom score (AM/PM).

The average morning PEF will be calculated as:

> (sum of morning PEF values in treatment period) / (number of morning e-Diary sessions completed during period).

The average evening PEF will be calculated analogously.

Daily asthma symptom score for day n will be the average of the evening score recorded for day n and the morning score for day n+1.

The average daily asthma symptom score will be calculated as:

(sum of daily values in treatment period) / (number of calculated daily values during period).

4.12.4 Fractional Exhaled Nitric Oxide

The analysis of change from baseline in log transformed FeNO will be performed as described for the primary endpoint in Section 4.11. These analyses will be done on the natural log scale and the results will be back-transformed to linear scale. Hence treatment effects will be presented in terms of Geometric LS means (GeoLSMeans) and treatment differences and associated CIs will be presented in terms of GeoLSMeans ratios. Due to the log-transformation, the GeoLSMeans represent a relative change from baseline rather than an absolute change from baseline.

Percentage change from baseline in FeNO at each week and average over the treatment period will be summarised by treatment group and the following summary statistics will be presented: n, geometric mean, GeoCV (%), median, minimum, and maximum.

For repeated follow-up post-baseline measurements that are taken on the same day and time as a scheduled visit and time point, the average response value of the morning assessments will be used. The average over the treatment period will be calculated from the subjects' average measurements of all assessments performed whilst subjects are on-treatment between Visit 3 and Visit 7.

All the efficacy variables will be presented in listings.

The following figures will be presented:

- In-clinic FeNO, individual subject data over time.
- Mean FeNO in-clinic absolute values (ppb) by week
- Mean FeNO in-clinic percentage change from baseline by week
- GeoLSMeans of the ratio (post/baseline) (+/- SE) in FeNO over time within each treatment group will be provided.

4.13 Exploratory CCI Variables (Part 1)

All the exploratory analysis will be presented based on FAS. The exploratory efficacy variables will be evaluated with descriptive statistics. All the efficacy variables will be presented in listings

4.13.1 CCI

CCI [redacted]

CCI [redacted]

CCI [redacted] CCI [redacted]
CCI [redacted]

4.13.2 Fractional Exhaled Nitric Oxide

A summary by treatment group (different doses of AZD1402, pooled AZD1402 and placebo) in terms of absolute values (ppb) at baseline (Visit 3) and at each day during treatment as well as the average over the treatment period, will be presented. Moreover, change from baseline at each visit during treatment and over the treatment period will be calculated as % change from baseline.

The average over the treatment will be calculated from the subjects' average measurements of all assessments performed whilst subjects are on-treatment.

Fractional exhaled nitric oxide (ppb) assessments will also be listed.

For FeNO at home assessments, the same summary described above for FeNO test (in-clinic assessments) will be presented. The average over the treatment will be calculated as the average of all assessments measurements for a given subject during the treatment period.

For repeated post-baseline FeNO test measurements that are taken on the same day and time as a scheduled visit and time point, the average response value of the morning pre-dose will be used.

For repeated post-baseline FeNO at home measurements that are taken on the same day and time, the highest results of the morning pre-dose will be used.

The following figures will be presented:

- In-clinic FeNO, individual subject data over time.
- Mean FeNO in-clinic absolute values (ppb) by day
- Mean FeNO in-clinic percentage change from baseline by day

4.13.3 Cough VAS

A summary by treatment group (different doses of AZD1402, pooled AZD1402 and placebo) in terms of absolute values at baseline, average over the treatment period, and change from baseline average over the treatment period, will be presented for cough VAS. Information from the VAS assessments will also be listed.

For cough VAS the average is defined as:

(sum of values in treatment period)/(number of e-Diary sessions completed during period)

The average over the treatment will be calculated as the average of all assessments measurements for a given subject during the treatment period.

All the efficacy variables will be presented in listings.

4.14 Exploratory CCI [redacted] Variables (Part 2)

All the exploratory analysis will be presented based on FAS.

4.14.1 CCI

CCI

CCI

4.14.2 CCI

CCI

4.15 Pharmacokinetics

4.15.1 Pharmacokinetic Concentrations

The PK parameters will be summarised and plotted separately for Part 1 and for Part 2 by dose level, nominal timepoints (PK Day) and for ADA status. Pharmacokinetic serum concentration data for AZD1402, will be listed by dose level (treatment) and subject. Listings will include actual sampling times relative to dose administration. Serum concentrations below the lower limit of quantification (LLOQ) will be presented as BLQ in the listings. Serum concentrations for AZD1402 will be summarised by dose level, and nominal timepoint (PK Day).

Summary statistics for the PK serum concentrations will be presented separately for Part 1 and for Part 2 by dose level, nominal timepoints (PK Day) and for ADA status and will include number of observations, number of observations below the LLOQ, geometric mean, Geometric CV% (calculated as: GeoCV% =SQRT(e^{s^2}-1)*100; where s is the SD of the log transformed values), geometric mean, arithmetic mean, arithmetic SD, median, minimum, and maximum. Any values that are not reportable or where no sample is available will be excluded from the summary tables. Three observations > LLOQ are required as a minimum for a serum concentration to be summarised. Where there are only 2 observations > LLOQ, these are presented as minimum and maximum and the other summary statistics are not calculated.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all derived PK concentrations without prior rounding.
- The mean, SD, geometric mean and median will be tabulated to 1 more significant digit compared to the source data, but with a maximum of 4 significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of 4 significant digits.

- Geometric CV% will be presented to 1 decimal place.

To visualise the comparison between dose levels the following descriptive PK graphs will be generated for each part:

- Geometric Mean (± gSD) AZD1402 serum concentration versus time by dose (linear scale and semi-log linear scale) presented for all doses overlaid on the same plot for a given PK Day (Day 1, Day 28). A different graph will be created for each ADA status.
- Geometric Mean (± gSD) AZD1402 serum concentration-time data (linear scale and semi-log linear scale) presented for PK Days 1 and 28 overlaid on the same plot for a given dose level. A different graph will be created for each ADA status.
- Individual Ctrough of AZD1402 will be plotted versus study day (linear scale and semi-log linear scale) for each dose level and all PK days (Day 1 to Day 56 for Part 1 and Day 1 to Day 39 for Part 2). A different graph will be created for each ADA status.
- Geometric mean (±gSD) AZD1402 Ctrough versus study day (linear scale and semi-log linear scale) will be presented for all study days (Day 1 to Day 56 for Part 1 and Day 1 to Day 39 for Part 2) and by dose overlaid on the same plot. A different graph will be created for each ADA status.
- Individual serum concentrations of AZD1402 versus actual time by dose will be plotted for each subject in linear and semi-log linear scale separately for Day 1 and Day 28.
- Individual serum concentrations of AZD1402 versus actual time by dose will be plotted for each Subject in linear and semi-log linear scale overlaid on the same figure for Day 1 and Day 28 (dose levels will be displayed separately).
- Box plot of Ctrough over time by ADA category.

4.15.2 Handling of Values Below the Limit of Quantification for Summarising and Presentation of Concentration Data

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as BLQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual serum concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings.

Serum concentrations that are BLQ, NR, or NS will be handled as follows for the provision of descriptive statistics:

- Any values report as NR or NS will be excluded from the summary tables and figures.
- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than half (but not all) of the values are BLQ, the geometric mean, Geometric mean/gD, Geometric mean * gSD and GeoCV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.
- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. The arithmetic mean, geometric mean, minimum, median, and maximum will be

reported as BLQ and the SD, GeoCV% and geometric mean / gSD and geometric mean * gSD as Not Applicable (NA).

- The number of BLQ values (n below LLOQ) will be reported for each time point.

Three observations > LLOQ are required as a minimum for a serum concentration to be summarised. If there are only 2 observations > LLOQ they are presented as minimum and maximum and the other summary statistics presented as NA.

Pharmacokinetic concentration and parameter data for subjects excluded from the PK set will be included in the data listings, but not in the descriptive or inferential statistics or in mean figures or combined individual figures.

4.15.3 Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by non-compartmental analysis methods from the concentration-time data using Phoenix® WinNonlin® (Version 8.1) or higher following these guidelines:

- Concentration data will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with the amount and concentration units, will be presented as they are received from the analytical laboratory.
- Cmax and tmax will be derived directly from the serum concentration-time profiles. For multiples peaks the highest post-dose concentration will be reported as Cmax. In the case that the multiple peaks are of equal magnitude, the earliest tmax will be reported.
- Serum concentrations which are BLQ from the time of pre-dose sampling (t = 0) up to the time of first quantifiable concentration will be set to a value of zero. After the first quantifiable concentration, any BLQ serum concentrations will be set to missing for all concentration profiles.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless there is a scientific rational not to do so, which will be documented in the CSR.
- Any embedded BLQ value (between 2 quantifiable concentrations) will be set to missing for the purposes of PK analysis.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- Terminal elimination half-life, calculated as $(\ln 2)/\lambda z$, will be estimated by log-linear LS regression of the terminal part of the concentration-time curve. The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations. A minimum of 3 data points following Cmax and including the last measurable concentration will be used in calculating λz. The duration of time over which λz should, where possible, span 3 half-lives. The adjusted correlation coefficient (Rsq adj) should be ≥ 0.8.
- AUCs (including AUClast and AUCτ) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up log down). The minimum requirement for the

calculation of AUC will be the inclusion of at least 3 consecutive serum concentrations above the LLOQ.

- If the concentration at the time of dosing is missing, then this will be set to 0.
- Data exclusions from analysis should be avoided. However, in clear cases of technical issues, such as documented sample mix up, bioanalytical error or mis-dosing, individual or subject level data may be excluded from summaries or summarised separately. Data exclusions will be agreed with the AstraZeneca Clinical Pharmacology Scientist and discussed in the CSR.
- Pharmacokinetic parameters associated with positive pre-dose value(s) of greater than 5% Cmax for the first dose may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the pharmacokineticist.

Pharmacokinetic parameters will be listed by subject and summarised by AZD1402 dose and study Part. Descriptive statistics for calculated PK parameters will include: n, mean, SD, geometric mean, GeoCV%, median, minimum and maximum values. For tmax, only median, minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than 3 individual PK parameters are available.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings for PK parameters:

- Individual PK parameters will be presented to 4 significant digits, with the exception of tmax, which will be presented to 2 decimal places.
- Parameters derived directly from source data (eg, Cmax,) shall be reported with the same precision as the source data (if this is not 4 significant digits).
- The mean, geometric mean, median, and SD values will be reported to 4 significant digits, all other descriptive statistics will be reported to 3 significant digits.
- For tmax, the minimum and maximum will be presented to 2 decimal places and all other descriptive statistics will be presented to 3 decimal places.
- Estimates and CIs in the form of percentages will be presented to 2 decimal places.

4.16 Immunogenicity Evaluation

Anti-drug antibodies will be summarised as categorical variables with the number and percentages with a positive result at the specific visit. Immunogenicity titre will be summarised descriptively as a continuous variable, only for ADA positive tests, with median, interquartile range, minimum, and maximum, at each analysis visit.

ADA will also be summarised based on the IS including the following:

- ADA positive at baseline and/or post-baseline (ADA prevalence).
- Treatment emergent (TE)-ADA positive (ADA incidence): defined as the sum of treatment-induced ADA positive and treatment-boosted ADA positive.
- Treatment-induced ADA positive: defined as ADA negative at baseline and post-baseline ADA positive.
- Treatment-boosted ADA positive: defined as ADA positive at baseline and boosted the pre-existing titre post-baseline ($\geqslant$ 4-fold increase).

- TE-ADA negative: defined as ADA positive but not fulfilling the definition of TE-ADA positive.
- Both baseline and post-baseline positive.
- Only baseline positive.
- ADA persistently positive: defined as either ADA negative at baseline and ADA positive at $\geqslant$ 2 post-baseline assessments, or ADA positive at last post-baseline assessment.
- ADA transiently positive: defined as ADA negative at baseline, having at least one post-baseline ADA positive assessment and not fulfilling the conditions of ADA persistently positive.
- TE-ADA positive with maximum titre > median of maximum titres.

Post-baseline includes on-treatment and follow-up phases.

The median of maximum titres is calculated based on the maximum titre for each ADA positive subject within each treatment group (including both baseline and post-baseline measurements).

All immunogenicity parameters will also be reported in listing. Days from previous dose of IP will be calculated as the ADA date minus date of previous dose. Days from previous dose of IP for ADA measured during pre-treatment period will be set to missing. Listings of all subjects excluded from the ADA analysis set will also be provided. Listing will be based on SS.

4.17 Safety Evaluation

All safety summaries and analyses will be based upon the SS as defined in Section 4.5.1 and will be presented by dose level of AZD1402, pooled AZD1402, and placebo and by study part.

In general, there will be no imputation of missing data for the safety analyses. All safety data (scheduled and unscheduled) will be presented in the data listings.

Baseline for safety evaluations will be the last value obtained before first study intervention.

4.17.1 Adverse Events/Serious Adverse Events

Adverse events will be coded using MedDRA latest available version.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of intensity, outcome, action taken with IP, and possible relationship to study drug (assessed by investigator). A by subject listing of all AE (including AEs before first dose of study medication) will be provided. This listing will include the following information: study period, verbatim term, MedDRA SOC, and preferred term, start date/time, end date/time, time from last dose, intensity, causality, action taken, whether the AE was classified as serious, the outcome of the AE and the concomitant or additional treatment given, if any. Any AE occurring before the first dose of IP and/or the AE assessments that are unresolved at the participant's last assessment in the study will be included in the data listings but will not be included in the summary tables of AEs.

Multiple occurrences of an AE in the same subject will only be counted once overall considering start date as the first day of first occurrence and stop date the last day of the last occurrence and the AE will assigned to the treatment of the first occurrence period study drug. Multiple occurrences of an AE in the same subject for the same treatment will only be counted once for that treatment.

The number of subjects will be tabulated also by SOC, preferred term, and treatment.

In the case that, during the study, a subject has more than 1 episode of the same preferred term with different levels of intensity, action taken, outcome causality or seriousness, then the maximum intensity level, action taken (ie, withdrawn) and outcome (ie, fatal), causality level (ie, related), or seriousness level (ie, serious), respectively will be used.

The following ordering will be used to define maximum intensity level, action taken, outcome causality level, or seriousness level:

- Intensity: Mild < Moderate < Severe
- Causality: No < Yes
- Seriousness: No < Yes
- Action taken: Unknown < Not applicable < Dose not changed < Drug interrupted < Drug withdrawn
- Outcome: Unknown < Recovered/resolved < Recovered/resolved with sequelae < Recovering/ resolving < Not recovered/not resolved < Fatal

A general summary of all AEs will show the number and percentage of subjects with:

- Any AE
- Any SAE
- Any SAE with outcome death
- Any AE leading to discontinuation of IP
- Any AE leading to withdrawal from study

An overview summary of AEs together with a presentation of AEs (event count) by preferred terms and sorted by decreasing frequency on preferred term will be also produced. In addition, an overview summary of the number and percentage of subjects with AEs and by SOC, preferred term, and treatment will be also presented by ADA status.

Additional tables will present the number and percentage of subjects with any AESI occurring after first dose (including infection, eosinophilia, and hypersensitivity events) and the in-clinic alerts with the individual occurrences in those categories.

The AESI presented in the table will be (for in-clinic assessments):

- FEV_1 drop $\geqslant$ 20% reduction from baseline as informed by in-clinic assessment: information extracted from the AE page on the eCRF.
- FEV_1 drop $\geqslant$ 30% reduction from baseline as informed by:
- in-clinic assessment.
- decline is sustained over 2 scheduled consecutive home assessments resulting in either dosing suspension or discontinuation (Part 2).
- Confirmed fever (> 38°C for > 4 hours)
- Wheeze*
- Cough*
- Dyspnoea/shortness of breath*

- Infection
- respiratory tract infection, ideally supported by pathogen identification and confirmation.
- COVID-19 infection.
- non-respiratory tract infection.

*Part 1: All new events of wheeze, cough, dyspnoea/shortness of breath.

Part 2: All new worsening events of wheeze, cough, dyspnoea/shortness of breath compared to baseline / individual pre-existing disease characteristics as judged by the Investigator.

In the event of suspected respiratory infection, pathogen identification include:

- SARS-CoV-2 PCR.
- Viral panel which may include but are not limited to influenza (all types), parainfluenza, respiratory syncytial virus, human metapneumovirus, adenovirus, and *Bordetella pertussis*.
- *Mycoplasma pneumonia* and *Chlamydophila pneumoniae* (sometimes included in viral panel).
- Bacterial swab to detect any growth which may include, but are not limited to Streptococcus, Klebsiella, Pneumoniae, Pseudomonas, *Staphylococcus aureus*, E.*Escherichia coli*, Citrobacter, Acinetobacter and *Haemophilus influenza*.

The number and percentage of subjects who experience one or more AEs will be tabulated by each study part, treatment group (dose level of AZD1402, pooled AZD1402, and placebo) and by:

- SOC and preferred term.
- SOC, preferred term, and maximum intensity.
- SOC, preferred term, and relationship to study intervention judged by investigator.

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and preferred term within SOC.

The tables of AE will include all the AEs with an onset date and time on or after the date and time of first dose of IP up to the end of treatment + 96 hours. Additional tables including all the AEs experienced after the IP until last follow-up (Day 56) and for ADA status will be reported for both Part 1 and Part 2.

Adverse events sorted by decreasing frequency and AEs leading to discontinuation of investigational product by SOC and preferred term will be summarised.

The number and percentage of subjects who experience 1 or more SAEs will be tabulated by treatment group (AZD1402 and placebo) and by SOC and preferred term and by SOC and preferred term and with outcome of death.

For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, a conservative approach for AE assessment (taking into account the worst case) will be followed.

Key subject information for participants experiencing SAE with outcome death, SAEs, and AEs leading to discontinuation of IP will be presented in a listing. All the AE will be included in the data listings.

For AEs with partial dates/times, worst case is always assumed; if possibly on-treatment, then on-treatment is assumed, on-treatment AEs will be considered to have the longest possible duration and off-treatment AEs will be considered to have the shortest possible duration. In accordance with this principle, any AEs with incomplete start and end dates/times will be treated as follows:

- AEs with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- AEs with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.
- AEs with partially known start dates/times will be treated as follows:

- If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and year in which IP was administered, then the day will be imputed with the first day on which IP was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
- If only the month is missing and the year is a year in which IP was administered, then the month will be imputed with the first month in which IP was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which IP was administered, then the month will also be imputed with JAN.
- If both the day and month is missing and the year is a year in which IP was administered, then the day and month will be imputed with the day and month of dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which IP was administered, then the day and month will also be imputed with 01JAN.
- If only the year is missing, then the year will be imputed with the year of dosing.

4.17.2 Clinical Laboratory Evaluation

Refer to Section 3.2.2.2 for the list of clinical safety laboratory tests to be performed and the SoA (Table 2 and Table 3), for timing and frequency.

Laboratory values and immune biomarkers measurements including IFNg, IL-10, IL-12p70, IL-13, IL-1b, IL-2, IL-4, IL-6, IL-8, TNFa, CRP, and IgE will be listed by subject and study time point including when possible changes from baseline.In case the units and the normal reference ranges are not the same for all subjects and assessments, units will be standardised to the same units and normalised to the same reference ranges.

The reference ranges and the values outside the clinical reference ranges will be presented and flagged in the data listings. The abnormal values will be flagged with ‘L’ for values below the lower limit of the clinical reference range and ‘H’ for values above the upper limit of the clinical reference range and included in the listings. The Investigator will assess whether the values outside the clinical reference range are clinically significant. Clinically significant laboratory values will be recorded by the investigator as AEs.

Descriptive statistics (for clinical chemistry, haematology coagulation parameters and immune biomarkers) will be presented separately for each part by treatment and time for both absolute values (N, mean, SD, median, minimum, maximum) and changes from baseline.

The following figures will be produced:

- Subject profile of haematology laboratory data (absolute values) for Part 1 and mean plots for Part 2.
- Subject profile of clinical chemistry laboratory data (absolute values) for Part 1 and mean plots for Part 2.
- Subject profile of immune biomarkers (absolute values) for Part 1 and Part 2
- Subject profile of CRP, absolute values and mean plots for Part 1 and Part 2.
- Mean immune biomarkers parameters by day, absolute values for Part 1 and Part 2.

Values of the form "< x" (ie, below the LLOQ) or "> x" (ie, above the upper limit of quantification [ULOQ]) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

Shift from baseline to maximum and to minimum on-treatment tables will be presented for laboratory parameters (chemistry, haematology and coagulation, urinalysis and immune biomarkers) including all blood white cells. The number of subjects with treatment emergent haematology abnormalities will be summarised.

The criteria for the haematology treatment emergent abnormalities (respect to baseline) are:

- Confirmed leucocyte count $< 2.0 \times 10^9$/L
- Confirmed neutrophil count $< 1.0 \times 10^9$/L
- Confirmed platelet count $< 75 \times 10^9$/L
- Confirmed lymphocyte count $< 0.5 \times 10^9$/L

Shift tables for the immune biomarkers IFNg, IL-10, IL-12p70, IL-13, IL-1b, IL-2, IL-4, IL-6, IL-8, TNFa, CRP, and IgE, will be presented by treatment and separately for each part.

Individual subject data where alanine aminotransferase/transaminase (ALT) and/or aspartate aminotransferase/transaminase (AST) and total bilirubin are elevated at any time will be listed (ie, ALT and/or AST $\geqslant 3 \times$ the upper limit of normal [ULN] and total bilirubin $\geqslant 2 \times$ ULN, at any time) to evaluate potential Hy's Law cases.

A figure for both ALT and AST versus total bilirubin expressed as multiple of ULN will be presented. Plot will be produced on the log scale, and reference lines will be included at 2xULN for total bilirubin and at 3 × ULN for ALT/AST.

Clinical laboratory data will be reported in the units provided by the clinical laboratory for the SRC meeting (if applicable), and in System International units in the CSR.

The number and percentage of subjects with a change from baseline in hsCRP higher then 5 and 10 mg/dL will be also reported by specified ADA status.

Figure for hsCRP over time by ADA status and by treatment group will be presented.

On-treatment and treatment emergent definition refer all the assessments with an onset date and time on or after the date and time of first dose of IP up to the end of treatment + 96 hours.

4.17.3 Vital Signs

Vital signs data will be listed by subject and visit including the planned time point, and reference ranges based on SS. Flag for a clinically significant assessment will be provided in the listing.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for absolute values and changes from baseline by treatment group (AZD1402 and placebo) and overall, per each study part. Vital sign shift tables from baseline to maximum on-treatment will be reported. The number of subjects with treatment emergent vital signs abnormalities will summarised considering the following table:

Vital sign		Observed value	Notable change from baseline
Systolic BP (mmHg)	High	⩾ 140	Increase of ⩾ 20
	Low	< 90	Decrease of ⩾ 20
Diastolic BP (mmHg)	High	⩾ 90	Increase of ⩾ 10
	Low	< 60	Decrease of ⩾ 10
Pulse Rate (bpm)	High	⩾ 110	Increase of ⩾ 20
	Low	< 50	Decrease of ⩾ 20
Respiratory Rate (breaths per minute)	High	> 20/min	
	Low	< 12/min	
Temperature (°C)			
	High	> 37.5	
	Low	< 35	

Abbreviations: BP = blood pressure; bpm = beats per minute.

On-treatment and treatment emergent definition refer all the assessments with an onset date and time on or after the date and time of first dose of IP up to the end of treatment + 96 hours.

4.17.4 Electrocardiogram

Standard safety 12-lead ECGs will be performed as shown in the SoA.

The following ECG parameters will be recorded:

- QRS interval (msec)
- RR-interval (msec)
- PR-interval (msec)
- QT interval (msec)
- QT-interval corrected using the Bazett correction formula (QTcB) (msec)
- QT-interval corrected using the Fridericia correction formula (QTcF) (msec)
- Heart rate (HR) (bpm)

The ECG will be evaluated by the investigator as 'Normal', 'Abnormal' or 'Borderline' and will be tabulated at baseline versus last value on-treatment by each dose and each part.

All ECG parameters will be listed by subject for each dose cohort and time point and each part. The baseline for the ECG measurements will be obtained pre-dose on Day 1.

Descriptive statistics (n, mean, SD, median, minimum, maximum) over time for absolute values and changes from baseline will be presented by each dose cohort and each Part. Categorical QT and QTc analyses will also be performed.

Shift tables will report the shift from baseline to the maximum value on-treatment: the number and percentage of subjects with QT/QTc intervals exceeding some predefined upper limits (eg, > 450 msec, > 480 msec, > 500 msec for absolute values as well as > 30 msec, > 60 msec for increase from baseline) of ECG parameters.

Abnormalities in electrocardiogram data will be listed based on SS.

On-treatment definition refer all the assessments with an onset date and time on or after the date and time of first dose of IP up to the end of treatment + 96 hours.

4.17.5 Spirometry

In-clinic and home spirometry values (FEV_1 and FVC) will be listed by subject and timepoint including absolute values, change from baseline, and percentage change from baseline.

Change from baseline will be calculated and presented by timepoint in each study part. Summary tabulations for absolute values, change from baseline and percentage change from baseline will be presented by treatment group (AZD1402, pooled AZD1402, and placebo) and overall, and by timepoint for in-clinic and e-Diary spirometry FEV_1. For in-clinic FVC similar tables will be presented.

For repeated post-baseline in-clinic spirometry morning measurements that are taken on the same day and time as a schedule visit and timepoint, the best response value of the morning pre-dose will be used.

For repeated post-baseline home spirometry measurements that are taken on the same day and time as a scheduled visit and time point, the highest results of the morning pre-dose will be used.

For repeated follow-up post-baseline in-clinic spirometry morning measurements that are taken on the same day and time as a scheduled visit and time point, the best response value of the morning assessments will be used.

For repeated follow-up post-baseline home spirometry measurements that are taken on the same day and time as a scheduled visit and time point, the highest results of the morning assessments will be used.

For Part 1, tables and figures presenting FEV_1 by study day will be based on the morning pre-dose values in case not differently indicated.

For Part 1 and/or Part 2 the following figures will be presented:

- In-clinic FEV_1 absolute values (L), individual subject by study day/week.

- In-clinic FEV_1 percentage change from baseline, individual subject data by study day/week.
- FEV_1 home spirometry absolute values (L), individual subject data by study day.
- FEV_1 home spirometry percentage change from baseline, individual subject data by study day.
- In-clinic FEV_1 mean absolute values (L) by study day/week and treatment group.
- In-clinic FEV_1 mean percentage change from baseline by study day/week and treatment group.
- FEV_1 home spirometry mean absolute values (L) by study day and treatment group.
- FEV_1 home spirometry mean percentage change from baseline by study day and treatment group.

The summary statistics for FEV_1 in-clinic spirometry and e-Diary spirometry will be presented separately.

For in-clinic FEV_1 for Part 1, the morning and evening post-dose percentage change from pre-dose by day, will also be summarised.

4.17.6 Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide will be listed by subject and timepoint including the date/time of the assessment, percentage changes from baseline and repeat/unscheduled measurements.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for absolute values and percentage changes from baseline will be presented by treatment group (AZD1402 and placebo) and by pooled AZD1402 groups.

4.18 Data Monitoring Committees

The SRC including the Sponsor study team will review PK and unblinded safety data following completion of Part 1a before progressing to Part 1b/2 and following completion of Part 1b. An unscheduled SRC meeting may also be held in the event of any safety or tolerability events requiring further review that may impact continuation of a cohort or the study, including unblinding data as required. All details on how the safety reviews are conducted are described in the SRC charter. A DSMB will oversee Part 2 of the study and review the unblinded interim outputs. In addition to a full DSMB periodic review of safety data, the committee can meet on an ad hoc basis. Details of the composition of the DSMB, frequency of meetings and remit can be found in the DSMB Charter. A separate review committee of AstraZeneca representatives will review the unblinded interim outputs for the interim analysis if performed.

4.19 Determination of Sample Size

In Part 1 (lead-in cohort), approximately 45 participants will be randomised. Part 1a will consist of 30 randomised participants and Part 1b will consist of 15 randomised participants. The sample size for Part 1 (lead-in cohort) is not based on any sample size calculation but was chosen to obtain reasonable evidence of safety and tolerability without exposing undue number of participants to the study intervention. In Part 2 (main cohort), 73 evaluable participants per treatment arm (CCI mg and placebo) will provide CCI% power using a 1-sided test and 5% significance level to detect a difference of 175 mL in FEV_1 between AZD1402 versus placebo. This is based on a SD of CCI mL, derived from an inter-participant SD of CCI mL in change from baseline to Week 4, adjusted for 4 repeated measurements and a correlation of CCI between weekly measurements. Assuming a dropout rate of

[redacted]%, approximately 80 evaluable participants per arm are needed. Due to the restricted recruitment into the [redacted]mg dose arm the precision of inference in terms of statistical power will be less than [redacted]% for the comparisons [redacted]mg versus placebo. A participant will be considered evaluable if he/she has a baseline and Week 4 FEV_1 results available. Part 2 will consist of approximately 165 participants.

4.20 Change in the Conduct of the Study or Planned Analysis

SAP updated for anticipated closure to remove some of the exploratory endpoints, the Per Protocol analysis and subgroup analysis.

4.21 References

Fuhlbrigge, et al. 2017
Fuhlbrigge AL, Bengtsson T, Peterson S, Jauhiainen A, Eriksson G, et al. A novel endpoint for exacerbations in asthma to accelerate clinical development: a post-hoc analysis of randomised controlled trials. The Lancet. Resp. Med. 2017: 5(7), 577-590.

5 APPENDICES

5.1 Schedule of Assessments

Table 2 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] - 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Signed informed consent	X														5.1
Admission			X					X							4.1.1
Discharge						X [e]			X						4.1.1
Optional residential stay (throughout Treatment Period)							X								4.1.1
Inclusion and exclusion criteria	X	X	X	X											5.1, 5.2
Demography	X														5.1
Medical/surgical history	X														5.1
Smoking history including cotinine testing	X							X							5.1
Asthma history	X														5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Height/weight [f]	X							X						X	8.2.1

Table 2 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] - 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Physical examination	X [g]			X [h]					X [h]			X [g]	X [h]	X [g]	8.2.1
Vital signs (blood pressure, pulse rate, temperature, respiratory rate) [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.2
Study drug inhalation training		X	X	X [j]											6.1.3
Home device dispensation (FeNO and spirometer)		X													6.1.2
Home device training (FeNO and spirometer)		X		X [j]											6.1.2
Rescue medication (eg, salbutamol) [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5.1
FeNO test (in-clinic) [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.3
FeNO at-home assessments (Niox Vero) [l, m]		X				X	X				X	X	X	X	8.1.3

Table 2 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] - 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Spirometry (FEV_1 and FVC) [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1
12-lead ECG [o]	X			X	X (Day 7)	X		X							8.2.3
ACQ-6	X	X		X	X (Day 7)	X	X (Day 20)	X				X			8.1.10
FEV_1/PEF (home device) [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1, 8.1.11
Cough VAS		X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.10
SPFQ (optional)		X				X						X		X	8.1.10
Assign e-Diary [q]	X														8.1.4
Dispense e-Diary [r]		X													8.1.4

Table 2 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] - 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Check e-Diary compliance			X	X	X	X	X	X	X	X	X	X	X	X	6.4.2
Check compliance with background medication			X	X	X	X	X	X	X	X	X	X	X	X	6.5
Collect e-Diary												X		X	8.1.4
Asthma symptom score and rescue medication use		X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.6, 8.1.7
Study drug dispensation						X									6.1
Study drug administration [s]	CCI														6.1.3
Drug accountability								X				X			6.2
Return unused medication and DPI								X				X			6.2
AEs [t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Blood samples for biochemistry	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for haematology	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for clotting profile	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for CRP (local laboratory) [w]			X	X	X	X	X	X	X	X	X	X	X	X	8.2.4
Blood sample for hs-CRP	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.5.1

Table 2 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] - 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Blood samples for safety immuno-biomarkers	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples allergen-specific IgE [x]			X												8.6.1
Blood samples for serum pregnancy test (all female participants)	X														5.1, 8.2.4
Blood samples for Hepatitis B (HBsAg, anti-HBs, anti-HBc), and C; HIV-1 and HIV-2; QFT for TB [y]	X														5.1, 8.2.4
Blood samples for PK measurements [z]				X	X	X	X	X	X	X	X	X	X	X	8.5.1
Blood samples for ADA [aa]				X		X	X (Day 20, 24)	X				X	X	X	8.5.2
CCI [bb]				X											8.6.2, 8.7
CCI				X (pre-dose)				X (pre-dose)				X		X	8.6.2
Urinalysis	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4

Table 2 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] - 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Blood samples for FSH (if needed to confirm postmenopausal status in female participants < 50 years and not on HRT)	X														5.1, 8.2.4
Urine pregnancy test (females of childbearing potential) [cc]			X					X				X		X	5.1, 8.2.4
Urine drug screen	X							X							5.2, 8.2.4
SARS-CoV-2 PCR [dd]	X	X	X [ee]	X	X	X	X	X	X	X	X	X	X	X	5.2, 8.2.4
SARS-CoV-2 serology [dd]	X											X		X	5.2, 8.2.4

Abbreviations: ACQ-6 = Asthma Control Questionnaire-6; ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CCI [redacted] COVID-19 = Coronavirus disease-2019; CRP =C-reactive protein; CSP = clinical study protocol; DPI = dry powder inhaler; ECG = electrocardiogram; e-Diary = electronic diary; ETV = early termination visit; FEV_1 = forced expiratory volume in 1 second; FeNO = fractional exhaled nitric oxide; FSH = follicle stimulating hormone; FVC = forced vital capacity; CCI [redacted] HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; CCI [redacted] HRT = hormone replacement therapy; hs-CRP = high sensitivity CRP; IgE = immunoglobulin E; IPD = Intervention Discontinuation Visit; CCI [redacted] PCR = polymerase chain reaction; PEF = peak expiratory flow; PK = pharmacokinetics; QFT = QuantiFERON; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SPFQ = Study Participant Feedback Questionnaire; SoA = Schedule of Activities; TB = tuberculosis; VAS = Visual Analogue Scale

[a] In-clinic outpatient visits during the Treatment Period will be scheduled so that they fall at the time of morning dose administration.

[b] Time between Visit 1 and Visit 2 may be extended up to 28 days upon input from the Study Physician.

[c] Visit 1 can be done on several/different days prior to Visit 2.

[d] Participants may be admitted on Day 27. Day 28 should be performed on the scheduled calendar day as far as possible; the -2-day window may be utilised only if required. If the -2-day window is utilised, all subsequent visits will be adjusted to follow time window between visits as specified in the SoA.

[e] Discharge on Day 14 after the morning post-dose procedures.

f Height only at Visit 1.

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

h A brief physical examination including an assessment of the general appearance, skin, abdomen, cardiovascular, and respiratory systems will be performed.

i Vital signs to be performed BID whilst participants are in-clinic. Vital signs will be measured pre-dose at the scheduled morning dose in-clinic visits and additionally prior to the evening dose if participants receive the evening dose at the clinic (eg, due to optional overnight stay).

j Refresher training as required.

k Rescue medication to be as necessary. Check if participant has enough rescue medicine for use at-home use and refill if necessary.

l FeNO will be measured pre-spirometry, pre-dose (as applicable), and pre-bronchodilation.

m FeNO assessments at home will only be performed (morning and evening) at non-clinic visit timepoints.

n In-clinic spirometry on Days 1 to 14 and Day 28 will be performed pre-dose and 2 h post-dose (± 15 min) in the morning (prior to taking controller medication) and on Days 1 to 13 pre-dose and 4 h post-dose (-2 h) in the evening. Where possible, all post-randomisation morning pre-dose clinic spirometry assessments should be performed within ± 30 minutes of the time that the randomisation spirometry was performed during the residential period. The evening pre-dose spirometry should also be performed within a ± 30 minutes window relative to the evening assessment timepoint. If patients remain in the unit without discharge to stay overnight during Days 14 to 27, a pre-dose and 2 h post-dose spirometry assessment will be performed in the morning (prior to taking controller medication) and pre-dose and 4 h (-2h) post-dose spirometry assessment in the evening. If patients are discharged and re-admitted to the unit for overnight stay on Days 15 to 27, the morning and evening post-dose spirometry assessment will be 4 h (-2h) post-dose (controller medication timing will remain unchanged from home dosing and controller medication will be taken directly after study intervention). At clinic visits with no overnight stay, morning pre-bronchodilator and 2 h post spirometry will be performed. The timing of controller medication and clinic post-dose spirometry assessments may be adjusted by the Sponsor.

o ECG will be measured before (within 75 min) and 1 hour (± 10 min) after administration of study intervention on visits as indicated.

p Home device spirometry will be performed pre-dose twice daily, including on in-clinic assessment days. On in-clinic assessment days, home spirometry may be performed up to 2 hours prior to dosing.

q At Visit 1 the e-Diary is set up, participants perform training and ACQ-6 and SNOT-22 is completed.

r The e-Diary will be completed twice daily during the Run-in, Treatment, and Follow-up Period.

s Study intervention will be administered CCI While at clinic, the study drug administration will be monitored by the site staff. Administration will be registered in the e-Diary by the participant.

t AEs will be collected from the time of informed consent. Unscheduled safety sampling may be performed at the discretion of the Investigator in the event of AEs/AESIs, including but not limited nasal swabs to confirm infection.

u Baseline safety sampling will be performed pre-dose on Day 1.

v Sampling on Days 2, 6, 8, 10, and 12.

w CRP must be done locally on Day -1 (may be performed on Day -2 for logistical reasons) to confirm eligibility as per inclusion criterion. It may be performed throughout the study in the event of AE/AESI as required to inform suspension/stopping criteria.

x Blood samples will be analysed for IgE if potential drug related IgE response is observed in any participant; may be collected on Day -1 or Day 1 pre-dose.

y PCR may be performed to confirm hepatitis B / hepatitis C status if required.

z Blood samples for PK measurements will be collected for all participants. Timing of samples: Day 1 pre-dose (-60 min), 1, 2, 3 (± 10 min), 4, 6, 8 (± 20 min) and 12 h (up to 1h prior to the next dose, must be before the subsequent dose); Day 28 pre-dose (-60 min), 1, 2, 3 (± 10 min), 4, 6, 8 (± 20 min), and 12h (± 1 h; single dose of AZD1402 only on Day 28). Pre-dose on Days 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 (up to 1 h prior to the next dose, must be before the subsequent dose), 29 (24 h ± 2 h after Day 28 dose), 30 (48 h ± 2.5 h after Day 28 dose), 32 (96 h ± 2.5 h after Day 28 dose), 39 (± 6 days), and 56 (± 4 days). Part Ib only: Day 20, 4 h post-morning dose (± 20 min). The PK sampling timepoints may be amended based on results from Part 1a/b. An unscheduled PK sample may be collected in the case of AEs and / or unscheduled safety blood sampling.

aa ADA sampling, pre-dose Day 1, Day 14, Day 20, Day 24 (Part 1b only) and Day 28 and on Follow-up/unscheduled visits. Participants CCI [redacted] An unscheduled ADA sample may also be collected in case of AEs/AESIs and/or unscheduled safety blood sampling.

bb Sample collection if consented only. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit.

cc All urine pregnancy tests will be done pre-dose.

dd SARS-CoV-2 serology at Screening, End of Trial and final Follow-up Visits; PCR is optional and may be performed centrally or at the local laboratory as clinically indicated and as per local guidelines for the duration of the study. Ad hoc nasal and/or throat-swab specimen is to be collected for the identification of a suspected respiratory infection during any visit. This may be performed locally, or if required by central laboratory.

ee May be performed on Day -2 for logistical reasons.

Table 3 Schedule of Activities Part 2

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
Signed informed consent	X											5.1
Inclusion and exclusion criteria	X	X	X									5.1, 5.2
Demography	X											5.1
Medical/surgical history	X											5.1
Smoking history including cotinine testing	X											5.1
Asthma history	X											5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X		6.5
Height/weight [d]	X						X					8.2.1
Physical examination	X [e]		X [f]				X [f]	X [f]	X [f]			8.2.1
Vital signs (blood pressure, pulse rate, temperature, respiratory rate) [g]	X	X	X	X	X	X	X	X	X	X		8.2.2
Study drug inhalation training		X	X [h]									6.1.3
Home device (spirometer) dispensation		X										6.1.2
Home device training (spirometer)		X	X [h]									6.1.2

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
Rescue medication (eg, salbutamol) [i]	X	X	X	X	X	X	X	X	X	X		6.5.1
FeNO test (in-clinic) [j]	X	X	X	X	X	X	X	X	X		X	8.1.3
Spirometry (FEV_1 and FVC) [k]	X	X	X	X	X	X	X	X	X		X	8.1.1
Reversibility test [l]	X											8.1.2
12-lead ECG [m]	X		X				X					8.2.3
ACQ-6	X	X	X	X	X	X	X	X	X			8.1.10
SPFQ (optional)		X			X			X		X [n]		8.1.10
FEV_1/PEF (home device) [o]		X	X	X	X	X	X		X			8.1.1, 8.1.11
Assign e-Diary [p]	X											8.1.4
Dispense e-Diary [q]		X										8.1.4
Check e-Diary compliance			X	X	X	X	X	X	X	X	X	6.4
Check compliance with background medication			X	X	X	X	X	X	X	X	X	8.1.4
Check compliance with study medication			X	X	X	X	X				X	
Collect e-Diary								X		X		8.1.5
Asthma symptom score and rescue use		X	X	X	X	X	X	X	X			8.1.6, 8.1.7
Study drug dispensation			X		X							6.1

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
Study drug administration [r]	CCI											6.1
Drug accountability					X		X	X				6.2
Return unused medication and inhaler					X		X	X				6.2
AE [s]	X	X	X	X	X	X	X	X	X	X	X	8.3
Blood samples for biochemistry	X		X [t]		X	X	X	X	X		X	8.2.4
Blood samples for haematology	X	X	X [t]		X	X	X	X	X		X	8.2.4
Blood samples for clotting profile	X											8.2.4
Blood sample for hs-CRP	X	X	X [t]		X	X	X	X	X		X	8.6.1
Blood samples for safety immuno-biomarkers	X		X [t]		X	X	X	X	X		X	8.2.5.1
Blood samples allergen-specific IgE [u]			X [u]									8.2.4
Blood samples for CRP (local laboratory) [v]			X	X	X	X	X	X	X	X	X	8.2.4
Blood samples for serum pregnancy test (all female participants)	X											5.1, 8.2.4
Blood samples for Hepatitis B (HBsAg, anti-HBs, anti-HBc), and C; HIV-1 and HIV-2; QFT for TB [w]	X											5.1, 8.2.4
Blood samples for PK measurements [x]			X		X	X	X	X	X		X	8.5.1
Blood samples for ADA [y]			X		X	X	X	X	X	X	X	8.5.1

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
CCI [z]			X									8.6.2, 8.7
CCI			X [aa]		X [aa]		X [aa]	X	X [aa]			8.6.1
CCI			X [aa]				X [aa]	X	X [aa]			8.6.1
CCI			X [aa]									
Urinalysis	X											8.2.4
Blood samples for FSH (if needed to confirm postmenopausal status in female participants < 50 years and not on HRT)	X											5.1, 8.2.4
Urine pregnancy test (females of childbearing potential) [bb]			X				X	X		X		5.1, 8.2.4
Urine drug screen	X											5.2, 8.2.4
SARS-CoV-2 PCR [cc]	X	X	X	X	X	X	X	X	X	X	X	5.2, 8.2.4
SARS-CoV-2 serology [cc]	X											5.2, 8.2.4

Abbreviations: ACQ-6 = Asthma Control Questionnaire-6; ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CCI COVID-19 = Coronavirus disease-2019; CRP =C-reactive protein; CSP = clinical study protocol; ECG = electrocardiogram; e-Diary = electronic diary; ETV = early termination visit; FEV_1 = forced expiratory volume in 1 second; FeNO = fractional exhaled nitric oxide; FSH = follicle stimulating hormone; FVC = forced vital capacity; CCI HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; CCI HRT = hormone replacement therapy; hs-CRP = high sensitivity CRP; IgE = immunoglobulin E; IPD = Intervention Discontinuation Visit; CCI PCR = polymerase chain reaction; PEF = peak expiratory flow; PK = pharmacokinetics: RNA = ribonucleic acid; QFT = QuantiFERON; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SPFQ = Study Participant Feedback Questionnaire; TB = tuberculosis

ff In-clinic outpatient visits during the Treatment Period will be scheduled so that they fall at the time of morning dose administration.

gg Time between Visit 1 and Visit 2 may be extended up to 28 days upon input from the Study Physician.

hh Visit 1 can be done on several/different days prior to Visit 2.

ii Height at Visit 1 only.

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

kk A brief physical examination including an assessment of the general appearance, skin, abdomen, cardiovascular, and respiratory systems will be performed.

ll Vital signs will be measured pre-dose at the scheduled morning dosing in-clinic visits.

mm Refresher training if required.

nn Check if participant has enough rescue medicine for use at-home use and refill if necessary.

oo FeNO will be measured pre-spirometry, pre-dose (as applicable), and pre-bronchodilation.

pp Spirometry will be performed 45 minutes and 15 minutes prior to first dose of study intervention on Day 1 and pre-dose at all other visits. If possible, all post-randomisation pre-dose morning clinic device spirometry assessments should be performed within ± 1.5 hours of the time that the 15 min prior to randomisation spirometry was performed.

qq Reversibility testing will be performed 15 to 30 minutes after inhalation of 400 µg of salbutamol.

rr ECG will be measured before study drug administration on Day 1 and Day 28 (within 75 min) and 1 hour (± 20 min) after administration of study intervention on Day 1 and Day 28.

ss SPFQ (optional) will not be completed at unscheduled visits.

tt At-home spirometry will be completed up to V8 and only to be completed at non-clinic visit timepoints.

uu At Visit 1 the e-Diary is set up, participants perform training and ACQ-6 is completed.

vv The e-Diary will be completed twice daily during the Run-in, Treatment, and Follow-up Period.

ww Study intervention will be administered CCI Date and time of administration at home will be registered in the e-Diary by the participant. Study drug administration at the clinic will be under supervision. The Day 28 dosing window ± 2 days should only be used if needed, and where possible to keep within ± 1 day.

xx SAEs will be collected from the time of informed consent. Non-serious AEs will be collected from the time of randomization. Unscheduled safety sampling may be performed at the discretion of the Investigator in the event of AEs/AESIs, including but not limited nasal swabs to confirm infection.

yy Baseline safety sampling will be performed pre-dose on Day 1.

zz Blood samples will be analysed for IgE if potential drug related IgE response is observed in any participant.

aaa Local CRP may be performed from Visit 3 and throughout the study in the event of AE/AESI as required to inform suspension/stopping criteria.

bbb PCR may be performed to confirm hepatitis B / hepatitis C status if required.

ccc Blood samples for PK measurements will be collected in all participants pre-dose at each visit, including unscheduled visits. Intense sampling may be performed in approximately 25% of participants per treatment arm (for example, 20 subjects in the CCI mg treatment arm). Timing of intense samples: Day 1: 1, 2, 3 (± 10 min), 6, and 8 h (± 20 min), Day 21 4 h post-morning dose (± 20 min) and Day 28 (last dose), 1, 2, 3 (± 10 min), 6, 8 (± 20 min), 24 (± 2 h), 48 (± 2.5 h), and 96 h (± 2.5 h; single dose of AZD1402 only on last day of dosing). PK sampling timepoints may be amended based on results from Part 1a/b. An unscheduled PK sample may be collected in the case of AEs and / or unscheduled safety blood sampling.

ddd ADA sampling, pre-dose Day 1, Day 14, Day 21, Day 28, and at the Follow-up Visits. An unscheduled ADA sample may also be collected in the case of AEs/AESIs and/or unscheduled safety blood sampling.

eee Sample collection only if consented. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit.

fff Proposed samples and times: Serum: Pre-dose Day 1, pre-dose Week 2, Week 4 and at Follow-up. CCI Pre-dose Day 1, and Week 4. CCI Pre-dose Day 1, Day 28, and Day 39. CCI Pre-dose Day 1.

ggg All urine pregnancy tests will be done pre-dose. In case of a positive result, a serum pregnancy test will be performed.

hhh SARS-CoV-2 serology at Screening; PCR is optional and may be performed centrally or at the local laboratory as clinically indicated and as per local guidelines for the duration of the study. Ad hoc nasal and/or throat-swab specimen is to be collected for the identification of a suspected respiratory infection during any visit. This may be performed locally, or if required by central laboratory.

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