A Single-Blind, Randomized, Placebo-Controlled 3-Part Study in Healthy Volunteers and Patients with Mild Asthma to Investigate the Safety, Tolerability and Pharmacokinetics of Inhaled AZD0449 Following Single and Multiple Ascending Doses and to Investigate the Anti-Inflammatory Effect of Inhaled AZD0449

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Statistical Analysis Plan: Final 1.0, 05 November 2021

Parexel International

AstraZenca

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Statistical Analysis Plan

Version: Final 1.0

Parexel Project Number: CCI

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

PPD
Global Product Statistician
AstraZeneca

Date

Parexel SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with CCI [redacted] and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: Biostatistics Lead

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CCI [redacted]

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 1.0	21 Aug 20	New document after approval of PA 7 and combining all studies parts in one file.
Draft 2.0	20 Jan 21	Updated as per Szilárd comments and as per PA8. Moreover, text for Interim Analysis section has been updated as per last discussion regarding this topic.
Draft 3.0	08 Feb 21	Tables 14.2.9.x have been included. IA text aligned with proposal for PA10.
Draft 4.0	01 Jul 21	PK section updated as per additional comments from AZ and Covance.
Draft 5.0	07 Jul 21	Updates for last comments from Covance.
Final 1.0	08 Jul 2021	Draft 5.0 has named to Final 1.0.

LIST OF ABBREVIATIONS

List and define all acronyms and abbreviations used in the document here. Abbreviations should be spelled out in full and the abbreviation indicated in parentheses at first appearance in the text. Abbreviations should appear in alphabetical order.

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
AUCinf/D	Dose normalized area under the plasma concentration-time curve from time zero to infinity
AUClast	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(0-24)/D	Dose normalized area under the plasma concentration-time curve from time zero up to 24 hours post-dose
AUC(0-24)	Area under the plasma concentration-time curve from time zero up to 24 hours post-dose
BDRM	Blinded data review meeting
BLQ	Below the lower limit of quantification
BMI	Body mass index
BP	Blood pressure
Bpm	Beats per minute
CI	Confidence interval
CL	Total body clearance of drug from plasma after intravascular administration (parent drug only)
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (parent drug only)
Cmax	Maximum observed plasma (peak) concentration
Cmax/D	Dose normalised maximum observed plasma (peak) concentration

Abbreviation / Acronym	Definition / Expansion
CPKA	Covance Clinical Pharmacology Alliance
CRF	Case Report Form
CS	Clinically significant
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
dECG	Digital electrocardiogram
DPI	Dry-powder inhaler
ECG	Electrocardiogram
CCI	[redacted]
CCI	[redacted]
EN	Enrolled analysis set
CCI	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
FEV	Forced vital capacity
FIH	First in human
CCI	[redacted]
FVC	Forced vital capacity
GGT	Gamma glutamyl transpeptidase
Hb	Hemoglobin
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Heart rate
hs-CRP	High-Sensitivity C-reactive protein
IA	Interim Analysis
ICF	Informed consent form

Abbreviation / Acronym	Definition / Expansion
ICH	International Council for Harmonization
CCI	[redacted]
IMP	Investigational Medicinal Product
IND	Investigational New Drug
CCI	[redacted]
IV	Intravenous
LLOQ	Lower limit of quantification
LLT	Lowest level term
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not available
OC	Observed cases
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PDF	Portable document format
PDS	Protocol deviation specification
PI	Principal Investigator
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PoM	Proof of mechanism
PPS	Per protocol analysis set
PR	The PR interval is the ECG interval measured until the onset of the QRS complex
PT	Preferred term
QRS	The ECG interval measured from the onset of the QRS complex to the J point
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave

Abbreviation / Acronym	Definition / Expansion
CCI	[redacted]
QTcF	QT corrected using Fridericia's formula
RBC	Red blood cell
REML	Restricted maximum likelihood
RR	The RR interval is measured as the time between corresponding points on 2 consecutive R waves on an ECG
RS	Randomized set
Rsq-adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation or single dose
SE	Standard error of the mean
SoA	Schedule of Assessments
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Scientific review committee
TBL	Total Bilirubin
TCA	Tricyclic anti-depressants
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures and listings
tlast	Time of last observed (quantifiable) concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
CCI	[redacted]
TSH	Thyroid stimulating hormone
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
ULN	Upper limit of normal

Abbreviation / Acronym	Definition / Expansion
Vz	Volume of distribution following intravenous administration (based on terminal phase) (parent drug only)
Vz/F	Apparent volume of distribution following extravascular administration (based on terminal phase) (parent drug only)
WAD	Windows Allowance Document
WBC	White blood cell
WHO-DD	World Health Organisation - Drug Dictionary
λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λz,N	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as ratio of t½λz
λz upper	Upper (later) t used for λz determination

1 INTRODUCTION

This Statistical Analysis Plan (SAP) details the statistical methodology to be used for analyzing 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 analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 1.0, September 18, 2018
- Protocol Amendment No. 1, Final 1.0, 23 October 2018
- Protocol Amendment No. 2, Final 1.0, 04 December 2018
- Protocol Amendment No. 3, Final 1.0, 09 May 2019
- Protocol Amendment No. 4, Final, 03 December 2019
- Protocol Amendment No. 5, Final, 11 February 2020
- Protocol Amendment No. 6, Final, 27 May 2020
- Protocol Amendment No. 7, Final, 26 June 2020
- Protocol Amendment No. 8, Final, 11 September 2020
- Protocol Amendment No. 9, Final, 08 December 2020

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 an 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 content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

2 STUDY OBJECTIVES

This study consists of three study parts: Part 1a, single ascending dose (SAD) in healthy volunteers; Part 1b, bioavailability in single intravenous (IV) dose cohorts; Part 2a, multiple ascending dose (MAD) in patients with asthma; Part 2b, MAD in healthy volunteers; Part 3a, proof of mechanism (PoM) in patients with mild asthma; Part 3b (optional), PoM in healthy volunteers.

2.1 Part 1a Objectives

2.1.1 Primary Objective

The primary objective of Part 1a is to assess the safety and tolerability of AZD0449 following inhaled administration of single ascending doses to healthy volunteers.

2.1.2 Secondary Objective

The secondary objective of Part 1a is to characterize the blood plasma PK of AZD0449 following inhaled administration of single ascending doses of AZD0449.

2.1.3 Exploratory Objectives

CCI

2.2 Part 1b Objectives

2.2.1 Primary Objective

The primary objective of Part 1b is to characterize the blood plasma pharmacokinetic (PK) of AZD0449 following intravenous (IV) administration of a single dose to healthy volunteers.

2.2.2 Secondary Objective

The secondary objective of Part 1b is to assess the safety and tolerability of AZD0449 following IV administration of 2 single doses to healthy volunteers.

2.2.3 Exploratory Objectives

CCI

- CCI [redacted]

2.3 Part 2a/b Objectives

2.3.1 Primary Objectives

The primary objective of Part 2a is to assess the safety and tolerability of AZD0449 following inhaled nebulized administration of multiple ascending doses in patients with mild asthma.

The primary objective of Part 2b is to assess the safety and tolerability of AZD0449 following inhaled nebulized administration of multiple ascending doses in healthy volunteers.

2.3.2 Secondary Objectives

The secondary objectives of Part 2a are the following:

- To characterize the blood plasma PK of AZD0449 following inhaled nebulized administration of multiple ascending doses in patients with mild asthma.
- To evaluate anti-inflammatory effect in patients with mild asthma.

The secondary objectives of Part 2b is to characterize the blood plasma PK of AZD0449 following inhaled nebulized administration of multiple ascending doses in healthy volunteers.

2.3.3 Exploratory Objectives

CCI [redacted]

- CCI [redacted]

2.4 Part 3a/b Objectives

2.4.1 Primary Objectives

The primary objective of Part 3a is to assess the safety and tolerability of AZD0449 following repeated inhaled administration using a dry-powder inhaler (DPI) in patients with mild asthma.

The primary objective of Part 3b is to assess the safety and tolerability of AZD0449 following repeated inhaled administration using a DPI in healthy volunteers.

2.4.2 Secondary Objectives

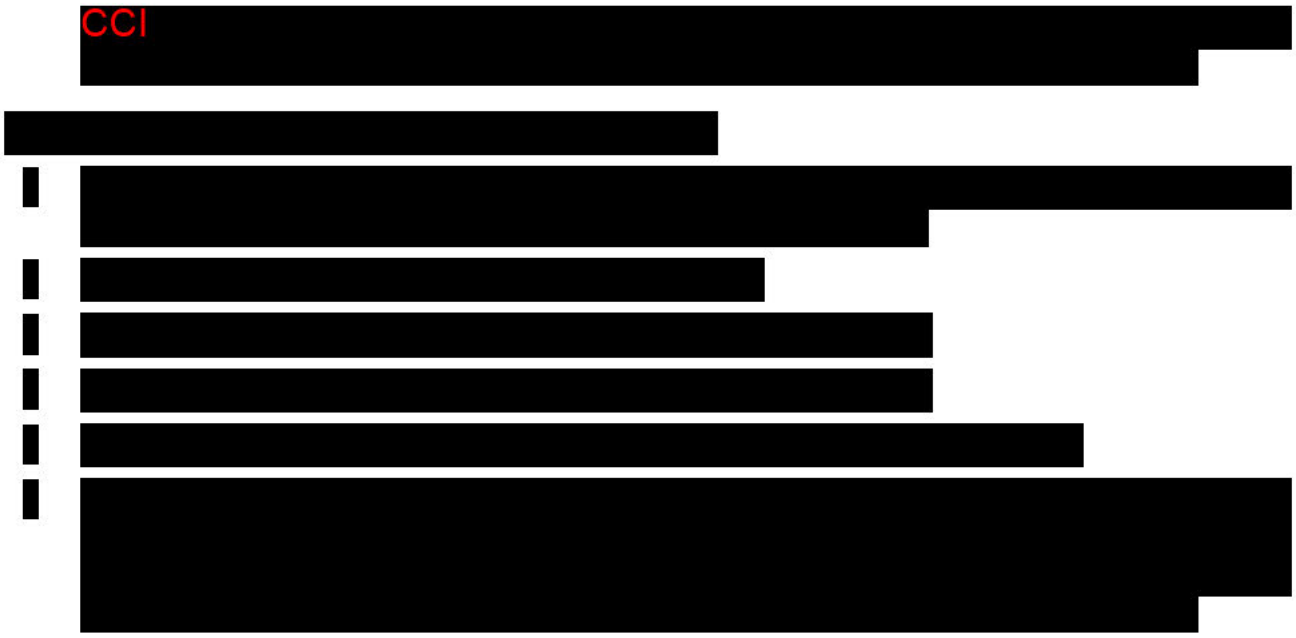
The secondary objectives of Part 3a are the following:

- To characterize the blood plasma PK of AZD0449 following repeated inhaled administration using a DPI in patients with mild asthma.
- To evaluate anti-inflammatory effect in patients with mild asthma.

The secondary objectives of Part 3b is to characterize the blood plasma PK of AZD0449 following repeated inhaled administration using a DPI in healthy volunteers.

2.4.3 Exploratory Objectives

CCI [redacted]



3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase I, first in human (FIH) study consisting of the following parts: Part 1a, Part 1b, Part 2a/b and Part 3a/b.

Part 1a of the study is a randomized, single-blind, placebo-controlled, SAD, sequential group design study performed at a single study center. Male and/or female healthy volunteers, aged 18 to 55 years will be included in this part of the study. This part of the study will be conducted in up to 72 volunteers.

Six inhaled dose levels of AZD0449 nebulized suspension are planned to be investigated in 6 cohorts. Depending on emerging safety and PK data, up to 3 additional inhaled dose levels (cohorts), within the pre-specified dose range, may be added at the discretion of the Sponsor. Within each cohort, 6 volunteers will be randomized to receive an inhaled dose of AZD0449 nebulized suspension and 2 volunteers will be randomized to receive inhaled placebo.

Dosing for each ascending dose cohort will start with 2 volunteers in a sentinel cohort, such that 1 volunteer will be randomized to receive AZD0449 nebulized suspension and 1 volunteer will be randomized to receive placebo

Intravenous (IV) dosing in Part 1b of the study will only be initiated after the completion of cohort 6 in Part 1a, or, if Part 1a is completed with less than 6 cohorts, after completion of the last cohort in Part 1a.

Part 1b is an open-label and consist of 2 dose cohorts (IV [redacted]) and be conducted in 12 healthy volunteers.

The first IV cohort will consist of the 6 volunteers that received an inhaled dose of AZD0449 nebulized suspension in Part 1a of the study. If Part 1b cannot be completed with 6 volunteers from Part 1a or if some of the data are considered not evaluable, up to 6 additional naïve volunteers may be enrolled.

All 6 volunteers will receive a single IV dose CCI of AZD0449 solution. Dosing will start with 1 healthy volunteer in a sentinel cohort, for more details see Section 3.1.2.1 of the CSP.

There will be a washout period of at least 2 weeks for the volunteers receiving both inhaled dosing in Part 1a and IV dosing in Part 1b.

A second IV dose cohort in Part 1b will be initiated after the evaluation of the PK and safety results from all cohorts in Part 1a and completion of the first IV dose cohort in Part 1b.

The second IV cohort will consist of the 6 healthy volunteers who have not previously participate in the study.

All 6 volunteers will receive a single IV dose CCI of AZD0449 solution. Dosing will start with 1 healthy volunteer in a sentinel cohort, for more details see Section 3.1.2.2 of the CSP.

Part 2a/b is a randomized, single-blind, placebo-controlled, MAD, sequential group design study performed at approximately 3 study centers. Subjects aged 18 to 55 years will be included in this part of the study. Unlike in Part 1a or Part 1b (first IV dose cohort), female subjects of childbearing potential may also be enrolled. This part of the study will recruit up to 56 subjects. A total of 26 evaluable subjects are needed for completion of Part 2a/b. Potentially, 30 extra subjects may be randomized to counteract drop-outs and allow for an extra cohort if needed.

Three dose levels of AZD0449 nebulized suspension are planned to be investigated in 3 cohorts. The cohorts could comprise either patients with mild asthma or healthy volunteers.

Part 2a includes cohorts 1 and 2, each comprising of 9 patients with mild asthma. Within each of these cohorts 6 patients will be randomized to receive AZD0449 nebulized suspension and 3 patients randomized to receive placebo. Additional cohorts with 9 patients could be added to study PK, pharmacodynamic (PD) and safety for doses lower than CCI

Part 2b will consist of 1 cohort of 8 healthy volunteers; 6 volunteers will be randomized to receive AZD0449 nebulized suspension and 2 volunteers will be randomized to receive placebo.

Dosing for each ascending dose cohort will start with 2 subjects in a sentinel cohort, such that 1 subject will be randomized to receive AZD0449 nebulized suspension and 1 subject will be randomized to placebo.

Part 3a/b of the study will be initiated after the completion of Part 2b. Part 3a/b is a randomized, single-blind, placebo-controlled, DPI/PoM study. Part 3 will be conducted in up to 36 patients with mild asthma (Part 3a) and 8 healthy volunteers (Part 3b, optional).

Part 3a will consist of 36 patients, aged 18 to 55 years, where 18 patients will be randomized to AZD0449 DPI and 18 patients to placebo. An Interim Analysis (IA) will be conducted when 9 patients

on each arm have completed the study (50% Part 3a). Should new data on the variability of the FeNO measurements emerge at the IA, the sample size in Part 3a could be changed.

If the optional Part 3b is conducted, it will comprise 8 healthy volunteers; 6 volunteers will be randomized to AZD0449 DPI and 2 volunteers to placebo.

Further details regarding the study design are provided in Section 3.1 of the CSP.

3.2 Endpoints and Associated Variables

3.2.1 Demographics and Baseline Characteristics

The following demographics and baseline characteristics variables will be collected: birth year, age at informed consent, gender, race, ethnicity, height (cm), weight (kg). Body mass index (BMI) will be derived.

3.2.2 Prior and Concomitant Medications

Medication started within 3 months before the first dose of Investigational Medicinal Product (IMP) as well as all medications taken during the conduct of the study will be recorded in the concomitant medication module of DataLabs®.

The following variables will be collected:

- Medication or therapy
- Start/stop dates and times, or ongoing
- Total daily dose/ dose per administration
- Units
- Frequency
- Route of administration/ inhalator type
- Indication
- Therapy reason, AE/medical history number

Prior and concomitant medication will be coded according to the World Health Organization Drug Dictionary (WHO DD), version September 2018.

3.2.3 Safety Variables

3.2.3.1 Adverse Events

Adverse Events (AEs) will be collected from the start of randomization throughout the treatment period up to and including the Follow-up Visit. Serious adverse events (SAEs) will be recorded from the time of informed consent. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. The following variables will be collected for each AE:

- Adverse event diagnosis/description

- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP (yes or no)
- Action taken with regard to investigational product
- Adverse event caused subject'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 aware of SAE
- Result in death
- Required or prolongs hospitalization
- Congenital anomaly or birth defect
- Life threatening
- Persistent or significant disability or incapacity
- Date of hospitalization/ discharge
- Primary/secondary cause of death
- Date of death
- Autopsy
- SAE caused by other medication, additional drug 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)

3.2.3.2 Laboratory Assessments

Laboratory assessments (hematology, clinical chemistry, urinalysis, serology, pregnancy tests, drug and alcohol abuse) will be performed at the time-points specified in the Schedule of Assessments (SoA), Section 6.1. The following parameters will be assessed:

Hematology	
White blood cell (WBC) count	Neutrophils absolute count
Red blood cell (RBC) count	Lymphocytes absolute count
Hemoglobin (Hb)	Monocytes absolute count
Hematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count
Mean corpuscular hemoglobin (MCH)	Platelets
Mean corpuscular hemoglobin concentration (MCHC)	Reticulocytes absolute count

Clinical Chemistry	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Uric acid	Gamma glutamyl transpeptidase (GGT)
Creatinine	Total Bilirubin (TBL)
Albumin	Unconjugated bilirubin
Calcium	Triglycerides
Phosphate	High-Sensitivity C-reactive protein (hs-CRP)
Glucose (fasting in plasma)	Thyroid-stimulating- hormone (TSH) [a]
Follicle stimulating hormone (FSH)[a] (post-menopausal females only)	

[a] Screening only

Urinalysis	
Glucose	Protein
Blood	
Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)	

Pregnancy test (females only)
Human beta chorionic gonadotrophin

Serology	
Human immunodeficiency virus (HIV) I and II	Hepatitis C Virus antibody
Hepatitis B surface antigen (HBsAg)	QuantiFERON® TB
Anti-HBc antibody [a]	

[a] Germany only

Drugs of Abuse and Alcohol	
Amphetamine	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates

Cocaine	Phencyclidine
Opiates	Urine Creatinine
Cotinine	Tricyclic anti-depressants (TCA)

COVID-19 Testing
Antibody, PCR, or alternative COVID-19 test will be conducted subject to local availability and site guidance

3.2.3.3 Vital Signs

The vital signs assessments will be performed at the time-points specified in the SoA, Section 6.1. The following variables will be collected after the subject has rested in the supine position for at least 10 minutes, in accordance with the site's standard operating procedure (SOPs):

- Systolic blood pressure (BP) (mmHg)
- Diastolic BP (mmHg)
- Pulse rate (bpm)
- Oral or tympanic body temperature (°C)
- Respiratory rate (breath per minute)

Flag for values outside reference range (L/H) and clinical significance (Yes/No) will be collected in the case report form (CRF).

3.2.3.4 Twelve-lead Safety Electrocardiogram

At the time-points specified in the SoA, Section 6.1. Twelve-lead electrocardiograms (ECGs) will be obtained after the subject rested in the supine position for at least 10 minutes. The principal investigator (PI) will judge the overall interpretation as normal or abnormal as well as details of abnormality. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the PI.

3.2.3.5 Electronic Capture of 12-lead Continuous Digital Electrocardiogram

The following digital electrocardiogram (dECG) variables will be reported by the AstraZeneca ECG Center:

- RR interval – the time between corresponding points on 2 consecutive R waves on ECG
- PR interval – ECG interval measured until the onset of the QRS complex
- QRS – ECG interval measured from the onset of the QRS complex to the J point
- QT interval – ECG interval measured from the onset of the QRS complex to the end of the T wave

The following parameters will be derived:

- QTcF – QT interval corrected for heart rate using Fridericia's formula

- HR – heart rate

3.2.3.6 Telemetry

A 12-lead real-time telemetry ECG will be performed at the time-points specified in the SoA, Section 6.1. The telemetry monitoring system will be reviewed by the Investigator and paper printouts of any clinically important events will be stored as source data. Overall telemetry evaluation (normal/ abnormal), reason of abnormality as well as flag for a clinical significance will be collected in the CRF.

3.2.3.7 Physical Findings

The full and brief physical examinations will be performed at the time-points outlined the SoA, Section 6.1.

Full
The complete physical examinations will include an assessment of the general appearance, skin, cardiovascular, respiratory, abdomen, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

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

The baseline/screening results of the physical examination 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.

3.2.3.8 Spirometry

Spirometry measurements, forced expiratory volume in one second (FEV_1) (L), forced vital capacity (FVC) (L) and FEV_1 % predicted, will be performed at the time-points outlined the SoA, Section 6.1.

3.2.3.9 Pulse Oximetry

Pulse oximetry will be performed and peripheral capillary oxygen saturation (SpO2) (%) will be measured at the time-points outlined the SoA, Section 6.1. Flag for values outside reference range (L/H) and clinical significance (Yes/No) will be collected in the CRF.

3.2.4 Pharmacokinetic Variables

Blood sampling for the determination of plasma concentrations AZD0449 will be collected for each study part at the time-points specified in the SoA, Section 6.1. CCI [redacted]

Where possible, the following PK parameters will be determined from the AZD0449 and CCI [redacted] plasma concentration-time data on Day 1 following the first AZD0449 dose and on Day 12 following once daily multiple AZD0449 dosing, as appropriate for each study part.

Following Inhaled dosing (Parts 1a, Part 2, and Part 3)	
Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or of maximum observed concentration following drug administration
AUClast	Area under the plasma concentration-curve from time zero to the time of last quantifiable concentration
AUC(0-24)	Area under the plasma concentration-time curve from time zero up to 24 hours post-dose
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
λz	Terminal elimination rate constant
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (parent drug only)
Vz/F	Apparent volume of distribution following extravascular administration (based on terminal phase) (parent drug only)
Cmax/D	Dose normalized maximum observed plasma concentration (calculated as Cmax divided by dose)
AUCinf/D	Dose normalized area under the plasma concentration-time curve from time zero to infinity (calculated as AUCinf divided by dose)
AUC(0-24)/D	Dose normalized area under the plasma concentration-curve from time zero up to 24 hours post-dose (calculated as AUC(0-24) divided by dose)
tlast	Time of last observed (quantifiable) concentration

Following Intravenous dosing (Parts 1b)	
Cmax	Maximum observed plasma (peak) drug concentration
tmax	Time to reach peak or of maximum observed concentration following drug administration
AUClast	Area under the plasma concentration-curve from time zero to the time of last quantifiable concentration
AUC(0-24)	Area under the plasma concentration-time curve from time zero up to 24 hours post-dose
AUCinf	Area under the plasma concentration-time curve from time zero to infinity
λz	Terminal elimination rate constant

t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
CL	Total body clearance of drug from plasma after intravascular (IV) administration (parent drug only)
Vz	Volume of distribution following intravenous (IV) administration (based on terminal phase) (parent drug only)
Cmax/D	Dose normalized maximum observed plasma concentration (calculated as Cmax divided by dose
AUCinf/D	Dose normalized area under the plasma concentration-time curve from time zero to infinity (calculated as AUCinf divided by dose)
AUC(0-24)/D	Dose normalized area under the plasma concentration-curve from time zero up to 24 hours post-dose (calculated as AUC(0-24) divided by dose)
tlast	Time of last observed (quantifiable) concentration

The following PK parameters will be calculated for diagnostic purposes and listed and summarized:

Diagnostic PK parameters	
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
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq-adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (λzN)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

The PK analyses of the plasma concentration data for AZD0449 CCI [redacted] will be performed by Covance Clinical Pharmacology Alliance (CPKA) on behalf of AstraZeneca, in accordance with current AZ Guidelines for Pharmacokinetic Evaluations in Clinical Studies.

PK parameters will be derived using non-compartmental analysis (NCA) methods with Phoenix® WinNonlin® (WNL) Version 8.1 or higher.

The actual sampling times recorded in the raw data will be used in the PK analysis. If actual times are missing, nominal times may be used. Nominal sampling times were used for interim plasma PK parameter calculations for the purpose of the scientific review committee (SRC) meetings.

Plasma concentrations below the lower limit of quantification (BLQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of 0. After this point, BLQ plasma concentrations will be set to missing for all concentration profiles. If 2 or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration-curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation of the PK parameters unless there is a scientific rationale not to do so; this will be documented in the PK analysis notes. If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

Dose normalised parameters will be determined by dividing the parameter by the dose.

Since each individual subject within a cohort will have a different actual infusion duration, a scheduled time for the End Of Infusion time for each Study Part and Cohort will be agreed to enable the concentrations for the samples taken at EOI, EOI+5 minutes, EOI+10 minutes and EOI+15 minutes to be included in the PK concentration descriptive statistics and corresponding figures. This infusion duration cannot be a value of '0', even where this is what has been recorded for some Study Parts and Cohorts, as this would mean the EOI sample and pre-dose sample would both have a time of zero which would cause a conflict in the PK NCA workflow and no PK parameters could therefore be determined for these subjects. Therefore, for the cohorts or subjects where the infusion duration is less than a minute and has been recorded as zero, a minimum infusion duration should be agreed e.g. 1 minute, to allow the EOI, EOI+5 min, EOI + 10 min and EOI+15 min samples to have actual elapsed times to be determined to use in the PK NCA.

3.2.5 Pharmacodynamic Variables

3.2.5.1 Fractional Exhaled of Nitric Oxide Part 2a and Part 3a

The FeNO (ppb) assessments will be performed at the time-points specified in the SoA, Section 6.1.

The measurement of exhaled NO is performed during regular slow exhalation.

CCI [redacted]

3.2.6 Exploratory Variables

CCI [redacted]

CCI

- CCI [redacted]

[redacted]

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

If not specified otherwise summary tables will be presented by treatment (dose level of AZD0449 or pooled placebo) and AZD0449 overall, where applicable, with descriptive statistics appropriate to the nature of the variables for each study part separately.

In general, for continuous variables, the number of non-missing observations, mean, standard deviation (SD), median, minimum (min) and maximum (max), will be presented; for categorical variables: counts (n) and percentages (%) (where specified) will be presented. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. These summaries will be provided by time-point of assessment as appropriate.

If at a given time-point, 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.

If not otherwise specified, subject listings will be presented as combined listings for all study parts whether the tables will be presented for each study part separately.

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

If not otherwise specified, baseline is defined as the last available pre-treatment assessment in each part of the study.

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

- **For repeated assessments at any time-point before first IMP administration in each part of the study** (including screening values and baseline): the latest assessment obtained per time-point will be used in the calculation of descriptive statistics
- **For repeated assessments at any time-point after first IMP in each part of the study** (including Follow-up visit): the first (non-missing) value after dosing will be used in the calculation descriptive statistics

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, FeNO, AUC(0-12) and any AE duration in case the time is included in the calculation of the duration.

4.3 Software

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

A complete set of raw data listings will be appended to the final CSR. All tables, figures and listings will be presented in portable document format (PDF) documents without any manual editing, i.e., they will appear unmodified as programmed by means of the statistical package.

4.4 Analysis Sets

4.4.1 Enrolled Analysis Set

The Enrolled analysis set (EN) will include all subjects who signed informed consent.

4.4.2 Randomized Analysis Set

The Randomized set (RS) will consist of all subjects randomized into the study.

4.4.3 Safety Analysis Set

The Safety analysis set (SAF) will include all subjects who received at least 1 dose of AZD0449 or placebo and for whom any safety post-dose data are available.

Unless otherwise stated the SAF will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP will also be presented using the SAF.

4.4.4 Pharmacokinetic Analysis Set

The PK analysis set (PKS) will consist of all subjects who received at least 1 dose of AZD0449 and who have evaluable PK data, with no major protocol deviations thought to impact on the analysis of the PK data. All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration at the blinded data review meeting when subjects are assigned to the PK analysis sets.

Data from subjects for whom the pre-dose concentration is > 5% of Cmax for the first dose of AZD0449 on Day 1 of the dosing period may be excluded from the descriptive and inferential statistical analyses and corresponding figures. If there are no other reportable PK data for a subject, then they may be excluded from the PK analysis set.

Any subjects to be excluded from the PK analysis set, PK data to be excluded from the descriptive and/or inferential statistical analyses or PK concentrations to be excluded from the PK non-compartmental analysis, will be agreed by the PK Scientist with the AZ Clinical Pharmacology

Scientist prior to the final PK analysis and handover of parameters to programming and identified in the PK flagging file and/or PK handover document. Current AZ guidance for PK data handling will be applied.

All available reportable concentration data and PK parameter data will be listed using the SAF. The available concentration data and PK parameter data for any subjects excluded from the PKS will be listed only. Concentration data for subjects excluded from the PKS will be presented in the individual figures of concentration versus time plots.

4.4.5 Full Analysis Set

The Full analysis set (FAS) will consist of all subjects randomized into the study, receiving at least 1 dose of IMP or placebo and having at least one 2-hour post-dose FeNO assessment after the first IMP intake.

4.4.6 Per Protocol Set

The Per Protocol analysis set (PPS) will consist of all subjects who belong to the FAS and who have no major protocol deviations that might impact results of FeNO.

4.5 Study Subjects

4.5.1 Disposition of Subjects

Subject disposition will be summarized for screening failures and randomized subjects separately. Screening failures data will be summarized on the EN. The following information will be provided with the percentage based on the number of screening failures:

- Number of subjects screened
- Number and percentage of screening failures including the reason of failing

Disposition summaries for randomized subjects will be presented by treatment group (each dose level of AZD0449, pooled placebo and pooled AZD0449) and include the following information:

- Number of subjects randomized
- Number and percentage of subjects who received treatment
- Number and percentage of subjects not receiving the treatment
- Number and percentage of subjects who completed the treatment
- Number and percentage of subjects who discontinued the treatment
- Number and percentage of subjects who completed the study
- Number and percentage of subjects who withdrawn from the study, including the reasons of withdrawal

Percentage will be based on number of subjects randomized.

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

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

Treatment duration (in days) will be calculated as follows:

Treatment duration (in days) = (date of last dose received - date of first dose received) + 1

The listing of subject disposition will include subject's randomization number, date of informed consent, date of randomization, the dose/treatment to which subject was randomized and study completion status.

The number and percentage of subjects included in each of the analysis sets will be summarized for all subjects based on the RS.

Subjects excluded from the analysis sets will be listed including the reason for exclusion based on the RS. Listing of data excluded from the PKS will be provided including the reason for exclusion based on the SAF.

4.5.2 Protocol Deviations

Protocol deviations are considered as any deviation from the CSP relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received, subject was not fasted as per the CSP requirements before and after dosing)
- Time window deviations for safety and/or PK assessments
- Subjects receiving prohibited concomitant medications
- Other procedural affecting the study endpoints and study conduct deviations recorded by the clinical unit on a CSP deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD), which stipulates tolerance windows for safety, PK and PD assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the blinded data review meeting (BDRM) before database hard lock in order to define the analysis sets for the study. The precise reasons for excluding patients from the study populations will be fully defined in the BDRM report.

Important protocol deviations will be summarized by treatment group (each dose level of AZD0449, pooled placebo, and pooled AZD0449) and will be listed for all randomized subjects.

4.6 Demographics and Baseline Characteristics

Demographic and baseline characteristic variables will be listed by subject and treatment group for all randomized subjects on each study part. Demographic and subject characteristics will be summarized by treatment (each dose level of AZD0449, pooled placebo and pooled AZD0449), for all subjects in the SAF, for part each study part separately. The denominator for percentages will be the number of subjects in the SAF for each treatment or for all subjects as applicable.

4.7 Medical History and Concomitant Illnesses

A listing of medical history data will be presented by subject and treatment group, for each study part and will include description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing if applicable).

4.8 Prior and Concomitant Medications

Medications that started and stopped prior to the first dose of IMP will be considered as prior medications. All medications taken at or after the first dosing are considered as concomitant (including medications that started before dosing and continued after).

Prior and concomitant medications will be listed by subject, treatment group and study part and will include the following information: reported name, anatomical therapeutic chemical (ATC) preferred term (PT), the route of administration, dose, frequency, start and end date/time and duration and indication.

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.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

4.9 Treatment Exposure / Compliance

4.9.1 Treatment Exposure

Drug administration dates and times and comments will be listed for each subject for each study part based on the SAF.

In addition, volume planned to be administrated, volume actually administrated, percentage of planned volume (defined as actual volume divided by planned volume and expressed as percentage), as well as interruption of infusion will be listed for Part 1b.

Date of inhaler nebulizer/DPI training will be presented in the listing for all study parts except Part 1b.

4.9.2 Compliance

Exposure in days and treatment compliance will be summarized using descriptive statistics by treatment (each dose level of AZD0449 and pooled placebo) for all subjects in the SAF for Part 2a/b and Part 3a/b. As well as number and percent of subjects in the following categories:

- <70% of compliance
- ≥70% and ≤130% of compliance
- >130% of compliance

Treatment compliance is defined as the number of days the subject received treatment divided by the number of days the subject should have received treatment (i.e. 12 days) multiplied by 100.

4.10 Safety Evaluation

All safety summaries and analyses will be based on the SAF.

4.10.1 Adverse Events

Adverse events (AE) with missing start dates/times will be handled as follows:

- Adverse events 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
- Adverse events with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and before dosing; in that case the start date will be imputed as the date of screening and a time of 00:00
- Adverse events 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 IMP was administered, then the day will be imputed with the first day on which IMP 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 IMP was administered, then the month will be imputed with the first month in which IMP 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 IMP 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 IMP 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 IMP 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

For the purposes of the AE summaries, AEs with unknown or missing intensity will be treated as 'severe' for the tabulations. Adverse events with unknown causality will be treated as with assessment 'yes' for the tabulations. Adverse events with unknown seriousness will be treated as serious for the tabulations. There will be no imputation of AE data for the data listings. All data will be listed as recorded in the CRF.

The number and percentage of subjects who experience AEs will be summarized by SOC, PT and will be presented by each dose level of AZD0449, pooled placebo, and pooled AZD0449 based on the SAF. The AEs that occur before first dosing will be excluded from the summary tables.

Summaries of AEs will include the following:

- Summary of incidence of AEs (overview including number and percentage of subjects with any AE, AEs leading to death, serious AEs, AEs leading to discontinuation of IMP and the study).
- Incidence of AEs
- Incidence of AEs by worst causality
- Incidence of AEs by maximum intensity

Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

In addition, an overview table with number of AEs will be provided, the summary will include the following:

- Number of all AEs
- Number of causally related AEs
- All AEs leading to death
- All causally related AEs leading to death
- All serious AEs
- All serious, causally related AEs leading to death
- All AEs leading to discontinuation of IMP
- All AE leading to withdrawal from study

Listings with the key information for serious AEs (SAEs), AEs leading to death and AEs leading to discontinuation of IMP will be provided for each study part. The following information will be included in the listings: verbatim term, PT, time from start date/time, end date/time and last dose, causality, action taken, seriousness and the outcome.

A listing of all AEs MedDRA coding will be presented by treatment and subject and will include verbatim name, lowest level term (LLT), PT and SOC. A separate listing of AEs severity and causality will be presented by treatment and subject and will include verbatim term, PT, severity, action taken, an AE outcome, causality, seriousness and information weather it led to withdrawal. A separate listing for AE onset and resolution will be presented as well.

4.10.2 Clinical Laboratory Evaluation

For by-visit summaries, the last non-missing assessment (including repeat assessments) recorded at each visit will be summarized. The baseline will be the last assessment available before the first IMP administration at each part of the study.

Hematology and clinical chemistry variables will be listed by treatment group, subject and timepoint and will include scheduled and repeat/unscheduled measurements. The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range and change from baseline.

Summary tabulations will be presented by treatment (each dose level of AZD0449, pooled placebo, and pooled AZD0449) based on the SAF, for each study part and include absolute values as well as absolute change from baseline. Changes from baseline will be calculated and presented for all post baseline timepoints including the Follow-up Visit.

Shift tables showing changes with respect to the normal ranges between baseline and any post-baseline at each study part visit will also be presented for select laboratory parameters (chemistry and hematology).

Any laboratory parameters with results from the laboratory given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (eg, <2.2 will be imputed as 2.2) for the descriptive statistics and changes from baseline.

Data listings for subjects that shows elevations in liver biochemistry (ie, occurrences of AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN) will be presented to evaluate HL.

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.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)
- Serology
- Drug of abuse, alcohol and cotinine

4.10.3 Vital Signs

The results of the vital signs measurements will be listed by treatment, subject and timepoint including the date/time of the assessment, flags for measurements that are outside the reference range (L or H, if applicable), changes from baseline and repeat/unscheduled measurements.

The baseline for vital signs measurements will be the last measurement before the first administration of IMP at each part of the study.

Descriptive statistics will be presented by treatment (each dose level of AZD0449, pooled placebo, and pooled AZD0449) and timepoint for both observed values and changes from baseline, for each part of the study.

4.10.4 Electrocardiography

4.10.4.1 Twelve-lead Safety Electrocardiogram

The twelve-lead ECG overall interpretation (normal/abnormal), specification of abnormality and clinical significance will be listed by treatment, subject and timepoint based on the SAF by each part of the study.

The number and percentage of subjects with clinically significant 12-lead ECG findings will be summarized by treatment group (each dose level of AZD0449, pooled placebo, and pooled AZD0449) by each day for Part 1a/b, Part 2a/b and Part 3a/b based on the SAF.

4.10.4.2 Electronic Capture of 12-lead Continuous Digital Electrocardiogram

The following parameters will be derived from the dECG:

- QTcF will be calculated as $\mathrm{QTcF} = \frac{\mathrm{QT}}{\sqrt[3]{\mathrm{RR}}}$ where the QT interval is in milliseconds and the RR interval is in seconds
- Heart rate will be calculated, based on the RR interval as HR= 60/RR interval, where the RR interval is in seconds

The dECG data will be smoothed on an individual basis before performing the derivations above and before calculation of any changes from baseline or descriptive statistics. For each subject it will be done as follows: the mean value of all the measurements will be taken for target timepoint recordings. At least 4 measurements with the time between the first and last record greater than 2.75 minutes for a target timepoint should be present or else, the smoothed value at the corresponding target timepoint will be set to missing.

The digital ECG results will be listed by treatment (each dose level of AZD0449 and pooled placebo), subject and timepoint and will include all individual and smoothed values of PR, RR, QRS, QT interval and the derived values of QTcF and HR. The changes from baseline for smoothed and derived parameters will be listed as well.

Descriptive statistics of smoothed PR, RR, QRS, QT values and derived QTcF and HR values as well as change from baseline will be summarized by treatment group (each dose level of AZD0449, pooled

placebo, and pooled AZD0449) and timepoint, for each study part. The baseline for the dECG measurements will be the smoothed pre-dose assessment on Day 1 for each part of the study.

Outliers with respect to QTcF will also be tabulated for the following categories

- Absolute value > 450 ms and ≤ 480 ms
- Absolute value > 480 ms and ≤ 500 ms
- Absolute value > 500 ms
- Increase from baseline > 30 ms and ≤ 60 ms
- Increase from baseline > 60 ms

The number and percentage of subjects with electrocardiogram outlier values by each dose level of AZD0449, pooled AZD0449 and pooled placebo will be provided for each study part.

4.10.4.3 Real Time ECG (Cardiac Telemetry)

Overall telemetry evaluation (normal/ abnormal), reason of abnormality as well as flag for a clinical significance will be listed by treatment group, subject and timepoint based on SAF.

4.10.5 Physical Examination

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

During the study conduct, any physical examination findings will not be listed or summarized in a separate listing or summary table. All physical examinations will be documented, summarized and listed as AEs.

4.10.6 Spirometry

For the spirometry variables the baseline value for each study part is defined as the pre-dose values recorded on Day 1 of each study period. If pre-dose value at Day 1 is missing, then the value at Day -1 of each study period for will be used as baseline value.

Spirometry values (FEV_1, FVC and FEV_1% predicted) will be listed by treatment group, subject and timepoint including absolute values, absolute and percentage changes from baseline.

Summary tabulations for absolute values and changes from baseline will be presented by treatment (each dose level of AZD0449, or pooled placebo, and pooled AZD0449) and timepoint for each study part for the SAF. For the purpose of the summary tabulations, where more than one FEV_1 or FVC measurements are assessed at a given time-point, the average FEV_1or FVC value at that time-point will be summarized.

4.10.7 Pulse Oximetry

Peripheral capillary oxygen saturation SpO2 (%) will be listed by treatment group, subject and timepoint including absolute values, changes from baseline and percentages changes from baseline as well as flag for values outside reference range and clinical significance.

The baseline for the measurements will be the pre-dose assessment on Day 1 (in each study part).

Summary tabulations for absolute values and changes from baseline will be presented by treatment (each dose level of AZD0449, or pooled placebo, and pooled AZD0449) and timepoint for each study part based on the SAF.

4.11 Pharmacokinetics

4.11.1 Presentation and Statistical Analysis of Pharmacokinetic Data

PK concentration and parameter data will be presented in accordance to the Standards for reporting clinical data in CSR or HLD v3.3, that include applicable descriptive statistics, handling of individual concentrations below the LLOQ for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data. A listing of PK blood sample collection times as well as derived sampling time deviations and all reportable concentrations will be presented for AZD0499 and CCI [redacted] as appropriate for each study part, based on the SAF.

Plasma concentrations will be summarized for the PKS for each time-point by study part, treatment (i.e. each dose level of each AZD0449 formulation) and study day, using protocol scheduled times and appropriate descriptive statistics.

The following rules will be followed with regards to the handling of individual concentrations below the lower limit of quantification (LLOQ) of the bioanalytical assay:

Individual concentrations below the LLOQ will be reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs.

Individual plasma 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.

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

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time-point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time-point where more than half of the values are NQ, the mean, SD, gmean, gmean - gSD, gmean + gSD and gCV% will be set to NC. The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.

- If all values are NQ at a time-point, no descriptive statistics will be calculated for that time-point. The gmean, mean, minimum, median and maximum will be reported as NQ and gmean -/+gSD, gCV% and SD as NC.
- The number of values below LLOQ (n <LLOQ) will be reported for each time-point. together with the total number of collected values (n).

Three observations ≥ LLOQ are required as a minimum for a plasma concentration to be summarized. Two observations ≥ LLOQ are presented as a minimum and maximum with the other summary statistics as not calculated (NC).

For summary figures geometric mean concentrations that are NQ will be handled as described for the descriptive statistics. If this handling results in a mean value of "NQ", then for visual presentation purposes the value plotted at that time point will be zero for linear plots and set to missing for semi logarithmic plots. The geometric mean concentration-time plots will include gmean-/+gSD error bars. Any error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual figures, concentrations that are NQ will be regarded as missing, with the exception of NQ values prior to the first quantifiable concentration in that profile which will be set to 0 for linear scale plots.

An LLOQ line should be included in all concentration-time-time plots except where there are multiple LLOQs for the same plot or for baseline corrected data,

All reportable PK parameters will be listed for AZD0449 CCI [redacted] as appropriate for each study part, based on the SAF. A separate listing will be provided for the diagnostic parameters.

Plasma PK parameters will be summarized for the PK analysis set by study part, dose level of AZD0449 and study day using appropriate descriptive statistics.
PK concentration and parameter data for subjects excluded from the PKS will be included in the data listings, but not in the descriptive or inferential statistics or in geometric mean figures or combined individual figures.

Individual plasma concentrations versus actual elapsed time after dose will be plotted on both the linear and semi-logarithmic scale for AZD0449 and CCI [redacted] with the Day 1 and Day 12 data overlaid on the same plot for study Parts 2 and Part 3.

Combined individual plasma concentration versus actual elapsed time after dose will be plotted on both the linear and semi-logarithmic scale for AZD0449 and CCI [redacted] Plots will be grouped by dose level of AZD0449 for each study part and study day.

Geometric mean (-/+ gSD) plasma concentration versus nominal sampling time will be plotted separately for each analyte, as appropriate, on both the linear and semi-logarithmic scale for each study part and study day, with all dose levels overlaid on the same plot for Part 1a Day 1 and Part 1b Day 1 and with Day 1 and Day 12 overlaid on the same plot for Part 2a (separately for each dose level), Part 2b, Part 3a and Part 3b.

Geometric mean plasma trough concentration for the MAD cohorts (Part 2a, Part 2b, Part 3a and Part 3b) will also be plotted versus study day with all dose levels overlaid on the same plot where applicable.

All plots will be based on the PKS, with the exception of individual plots by subject, which will be based on the SAF.

Precision and Rounding Rules
PK concentration data will be presented in the listings to the same number of significant digits as the data received from the bioanalytical laboratory (usually to 3 significant figures) and against the same units as received.

The following descriptive statistics will be presented for the plasma PK concentration data :

- n
- n < LLOQ
- arithmetic mean (mean)
- standard deviation (SD)
- geometric mean (gmean)
- gmean -/+geometric SD (gmean - gSD and gmean + gSD)
- geometric coefficient of variance (%) (gCV%)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as the exponential of the arithmetic mean calculated from data on a log scale. The gCV% is calculated as $100 \cdot \sqrt{\left(exp\left(s_g^2\right) - 1\right)}$ where s_g is the SD of the data on a log scale.

The gmean -/+ gSD are calculated as:
gmean - gSD: exp(mean(log(PK Conc)) – std(log(PK Conc))),
gmean + gSD: exp(mean(log(PK Conc)) + std(log(PK Conc))).

PK concentration descriptive statistics will all be presented to 4 significant figures with the exception of the min and max which will be presented to 3 significant figures and n and n <LLOQ which will be presented as integers. The minimum values in the PK concentration descriptive statistics will present NQ instead of the LLOQ value (where needed).

The plasma PK parameters, will all be presented to 3 significant figures in the listings with the exception of:

- Cmax which will be presented to the same number of significant figures as received from the bioanalytical laboratory
- tmax, tlast, λ lower and λ upper will be presented as received in the data
- λz,N will be presented as an integer (no decimals)

The descriptive statistics presented in the listings for all PK parameters will be n, arithmetic mean, SD, gmean, gmean - gSD, gmean + gSD, gCV%, median, min and max with the exception of:

- The diagnostic PK parameters (AUCextr, Rsq-adj, λz span ratio) which will present n, arithmetic mean, SD, median, min, max.
- tmax, λz lower, λz upper, tlast and λzN which will present n, median, min and max.

The descriptive statistics for PK parameter data will be presented to 4 significant figures (as an exception min and max that will be presented to 3 significant figures) apart from the following:

- tmax, tlast, λz lower and λz upper which will be presented as received in the data
- number of values (n) and λzN which will be presented as an integer
- an extra digit of precision will be added (typically four significant digits in total) for reporting of the geometric least-squares (LS) means and bounds of all confidence intervals (CI) within inferential analyses
- ratios and any corresponding CI values which are obtained during inferential statistical analysis shall be reported as a percent with at least four decimal places (e.g., 0.9999).
- p values that are smaller than 0.0001 will be presented as <0.00001

For the calculation of summary statistics of PK parameters, all not reportable (NR) and not calculated (NC) values will be set to missing. Three reportable values are required as a minimum for a PK parameter to be summarised. Two values are presented as a min and max with the other summary statistics as NC. If one or more values for a given parameter is zero (or imputed with zero), then no geometric statistics will be calculated for that parameter and the results for geometric statistics will be set to not applicable (NA).

4.11.2 Inferential Statistical Analysis of Pharmacokinetic Data

The power model will be used for the analysis of dose-proportionality for AZD0449 in Part 1a following a single dose on study Day 1 using the PK parameters Cmax, AUCinf and AUC(0-24 for all dose levels. The power model is denoted as $y=\alpha * dose^{\beta}$, where "y" refers to the PK parameter under consideration.

Dose-proportionality will be assessed via least squares (LS) linear regression of the log-transformed PK parameters versus the log-transformed dose, ie, log (PK parameter) = $\alpha+\beta\log(Dose)$. An estimate of the slope and intercept of the regression line and the corresponding 2-sided 95% confidence interval (CI) for the slope will be obtained and tabulated for Cmax,,AUCinf and AUC(0-24.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. The following SAS code will be used:

```
PROC MIXED DATA = <data>;
  MODEL <log_var> = <log_Dose> / CL ALPHA=0.05 SOLUTION DDFM=KR;
RUN;
```

Separate scatter plots for each of the log-transformed AZD0449 PK parameters versus log-transformed dose (Cmax, AUCinf and AUC(0-24)) will be presented with the regression line from the analysis overlaid on the same plot.

In addition, separate figures for each of the dose normalized AZD0449 parameters (Cmax, AUCinf and AUC(0-24) for Day 1 and Cmax and AUC(0-24) for Day 12) versus dose, showing individual and geometric mean values for each dose level, will be presented separately for Part 1a Day 1, Part 1b Day 1, Part 2a Day 1 and Part 2a Day 12, to visually demonstrate dose-proportionality.

4.12 Pharmacodynamics

4.12.1 Fractional Exhaled Nitric Oxide Analysis (FeNO) – Part 2a and Part 3a

The change from baseline in 2 hours post-dose log FeNO level to Day 12, will be analyzed based on MMRM using all post-baseline 2 hours post-dose FeNO assessments. Baseline will be defined as mean FeNO value at Day -1. The model will include the fixed, categorical effects of treatment, Day, and treatment-by-day interaction, as well as the continuous, fixed covariate of baseline FeNO value. Patient will be included as a random effect. This analysis will be based on the FAS. Analyses will be performed on the log-transformed FeNO data to normalize the skewed distribution of this endpoint. Change from baseline will be calculated based on the log-transformed data.

The within-patient correlation will be modeled using the unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be performed using only the observed cases (OC) without imputation of missing values. If the model does not converge, then the compound symmetry covariance structure will be used. Restricted maximum likelihood method will be used for estimation.

Treatment effect and treatment differences will be estimated using contrasts of the LS means on the correspondent treatment-by-day interaction, along with their standard error (SE) and 2-sided 90% CI, and the p-value corresponding to the treatment group difference.

The estimated treatment differences and the 90% CIs on the log scale will be back-transformed to obtain the geometric mean ratios for two groups compared. The geometric LS means and its 90% CIs, geometric LS means ratio between the treatments and its 90% CIs will be tabulated.

The same model will be used to evaluate treatment effect between the groups in Part 2a and Part 3a.

The following treatment groups will be compared at Part 2a:

- AZD0449 CCI (Part 2a Cohort 1) and CCI (Part 2a Cohort 2)
- pooled placebo (Part 2a Cohort 1 to 2)

The following treatment groups will be compared at Part 3a:

- DPI AZD0449 CCI
- placebo

In addition, for robustness of results, treatment effect of the change from baseline in 2 hours post-dose log FeNO level at Day 12 will be analyzed using analysis of covariance (ANCOVA) with treatment as a fixed effect, and baseline FeNO value as a covariate. The last observation carried forward (LOCF) method will be used to deal with missing values. Furthermore, both analyses will be repeated on PP. No multiplicity adjustments will be applied.

In addition, as sensitivity analysis, the change from baseline in area under the 12-hour FeNO curve to Day 12 (AUC(0-12)) will be analyzed using the same methods as the change from baseline in 2 hours post-dose FeNO level to 12 days. Baseline value will be defined as AUC(0-12) at Day -1. The AUC(0-12) will be calculated using linear trapezoidal rule and actual time based on pre-dose, 30min, 2, 6 and 12h post dose (or corresponding clock time on Day -1) FeNO assessments. FeNO AUC(0-12) will be calculated , if at least 3 of the 5 FeNO values are available, including FeNO pre-dose and 12 hours assessment. Furthermore, there should be no two consecutive time-points missing. If these criteria are fulfilled, missing values will be replaced by linear interpolation.

FeNO values will be listed by subject, day and time-point including absolute values, absolute and relative changes (in percentage) from baseline. Summary tabulations as well as gmean for absolute values and changes from baseline will be presented by treatment (each dose level of AZD0449, and pooled placebo), day and time-point for the FAS and PPS.

FeNO AUC(0-12) will be listed by subject and study day including absolute values and absolutely and relative change from baseline. Descriptive statistics of FeNO AUC(0-12) including change from baseline at each study day will be presented by treatment (each dose level of AZD0449, and pooled placebo) and day for the FAS and PPS.

Line plots for relative change from baseline in gmeans of 2h post-dose FeNO values and FeNO AUC(0-12) at each post baseline visit until Follow-up visit (Day 22), will be presented by each dose level and pooled placebo. The corresponding 90% CI for each timepoint will be presented. The change at Day 12 will be marked in the graph.

CCI [redacted]

4.13 Analysis of Exploratory Data

CCI [redacted]

CCI

[redacted]

4.14 Other Analyses

A listing of liver diagnostic investigations for potential Hy's Law (HL), liver risk factors and life style events as well as liver signs and symptoms will be listed by subjects with data available.

4.15 Determination of Sample Size

This is a Phase I study to investigate the safety and tolerability of a novel compound. The sample size was chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of subjects to the compound at this phase of clinical development.

Previous experience in Phase I studies has shown that the sample size being proposed is reasonable to accomplish the objectives of the study. Thus, no formal sample size calculation was done for Part 1 and the non-PoM cohorts in Part 2a/b and Part 3.

For Part 3a (PoM cohort):

- Endpoint: change from baseline in exhaled FeNO (log scale) while receiving multiple inhaled doses of AZD0449, in active and placebo arms
- Treatment difference (Treatment – Placebo) of change from baseline of mean Log FeNO, equivalent to a 25% reduction of the ratio of geometric mean

For Part 3a, assuming a log mean baseline FeNO level of 4.24 with SD of 0.38 (geometric coefficient of variation [GCV]=39.4%) and a correlation between baseline and last day of study data of 0.7, as

suggested by previous studies, the required sample size for a 25% absolute reduction in the ratio of geometric means (a 0.288 reduction of the mean log FeNO levels) is 18 evaluable patients per arm using a one-sided test at 5% significance level.

The current design presents an opportunity to perform a sample size calculation at an IA taking place when approximately half the data from Part 3a is available. If the actual estimate of baseline FeNO SD is higher than expected, reaching SD=0.55, the sample size of the PoM cohort in Part 3a will be potentially increased up to n=26 per arm.

Should the variation be even higher requiring adjustments beyond this, an amendment will be submitted.

4.16 Interim Analysis and IND submission

An unblinded IA will be performed when approximately 50% of the patients in have completed Part 3a. The collected data will be used to inform various decisions or actions such as assessing the efficacy of AZD0449 in an unblinded manner and to perform an unblinded sample size re-estimation.

For this IA, outputs for safety and FeNO data from all MAD cohorts up to that time points will be provided. Considering the SD observed for the FeNO endpoint, a decision will be made on either additional subjects than those described in section 4.14 should be included or not.

In order to have the required for the Investigational New Drug (IND) submission on December 2020, prior to the achievement of the data-cut for the IA, outputs for safety and FeNO data will be delivered for study Part 1a/b, Part 2a/b and Part 3b. Hence, at the time of the IA only outputs for study Part 3a will be delivered.

The outputs that will be delivered between IND submission and IA will be the followings according to TFLs shells draft 2.0:

- Table 14.2.5.1 and Table 14.2.5.2: Summary of FeNO (Full analysis set)
- Table 14.2.6.1 and Table 14.2.6.2: Summary of FeNO (AUC(0-12)) (Full analysis set)
- Table 14.2.7.1 and Table 14.2.7.2: FeNO, change from baseline in 2 hours post-dose, linear mixed model with observed cases (Full analysis set)
- Table 14.2.8.1 and Table 14.2.8.2: FeNO (AUC(0-12)), change from baseline in 2 hours post-dose, linear mixed model with observed cases (Full analysis set)
- Table 14.2.9.1 and Table 14.2.9.2: FeNO, change from baseline in 2 hours post-dose, linear mixed model with observed cases (LS means ratio) (Full analysis set)
- Figure 14.2.5.1 Geometric mean (90% CI) of change from baseline of 2h post-dose FeNO values versus study day by treatment group (Full analysis set)
- Table 14.3.1.1.1 through Table 14.3.1.1.6: Summary of number (%) of subjects who had at least one adverse event in any category (Safety analysis set)
- Table 14.3.1.2.1 through Table 14.3.1.2.6: Adverse events in any category – episode level (Safety analysis set)
- Table 14.3.1.3.1 through Table 14.3.1.3.6: Number (%) of subjects who had at least one adverse event, by preferred term, arranged by system organ class (Safety analysis set)
- Table 14.3.1.4.1 through Table 14.3.1.4.6: Number (%) of subjects who had at least one adverse event by preferred term, presented by investigator's causality assessment (Safety analysis set)

- Table 14.3.5.1.1 through Table 14.3.5.1.6: Descriptive statistics for Haematology laboratory results and change from baseline results (Safety analysis set)
- Table 14.3.5.2.1 through Table 14.3.5.2.6: Descriptive statistics for Clinical Chemistry laboratory results and change from baseline results (Safety analysis set)
- Table 14.3.6.1.1 through Table 14.3.6.1.6: Descriptive statistics for vital signs and change from baseline results (Safety analysis set)
- Table 14.3.7.1.1 through Table 14.3.7.1.6: Descriptive statistics for electrocardiogram results and change from baseline results (Safety analysis set): digital ECGs
- Table 14.3.8.1.1 through Table 14.3.8.1.6: Summary of spirometry and absolute and percentage change from baseline (Safety analysis set)

5 REFERENCES

Not applicable.

6 APPENDICES

6.1 Schedule of Assessments

Table 6.1 Schedule of Assessments Part 1a (SAD)

Schedule of Assessments Part 1a (SAD)						
Assessments	**Screening**	**Treatment Period**			**Follow-up Visit**	**Comments**
	Days -28 to--2	**Day -1**	**Days 1 to 3 [a]**	**Day 4 [a]**	**(6±1 days post-dose)**	
Informed consent	X					Includes optional genetic consent
Inclusion/exclusion criteria	X	X				
Demographic data	X					
Medical history	X					
Drug, alcohol and cotinine screen	X	X				
Serology	X					
QuantiFERON® TB	X					
Follicle-stimulating hormone testing	X					Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:						
Admission		X				
Discharge				X		At least 60 h post-dose, may be extended up to 96 h post-dose depending on emerging data
Non-residential visit	X				X	
Investigational Medicinal Product Administration:						
Inhaler Nebulizer Training		X				
Randomization			Day 1			
AZD0449/Placebo administration via nebulizer			Day 1 (0 h) [b]			
Safety and Tolerability:						
Adverse event questioning	Only SAEs	Only SAEs	X	X	X	

Schedule of Assessments Part 1a (SAD)						
Assessments	**Screening**	**Treatment Period**			**Follow-up Visit**	**Comments**
	Days -28 to--2	**Day -1**	**Days 1 to 3** [a]	**Day 4** [a]	**(6±1 days post-dose)**	
Spirometry	X	X	X	X	X	Day 1: Pre-dose and 30 min, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 4: 72 h post-dose
Pulse oximetry	X	X	X	X	X	**Cohorts 1-4:** Day 1: Pre-dose and 30 min, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 4: 72 h post-dose **Cohorts 5-6:** Day 1: Pre-dose, 1 h, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 4: 72 h post-dose
Blood pressure, pulse and respiratory rate (supine) and body temperature	X	X	X	X	X	**Cohorts 1-4:** Day 1: Pre-dose and 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose **Cohorts 5-6:** Day 1: Pre-dose and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose
12-lead dECG			X			See Table 3.2-8 from the CSP

Schedule of Assessments Part 1a (SAD)						
Assessments	**Screening**	**Treatment Period**			**Follow-up Visit**	**Comments**
	Days -28 to--2	**Day -1**	**Days 1 to 3 [a]**	**Day 4 [a]**	**(6±1 days post-dose)**	
12-lead safety ECG	X	X	X		X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide, see Table 3.2-8 from the CSP
Telemetry		X	X			Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2)
Height, weight and BMI	X	X				
Clinical laboratory evaluations	X	X	X	X	X	Day 2: 24 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose All samples will be collected after a 10 h fasting period. If the assessment period is extended, Day 4 assessments will be performed on the day the healthy volunteer are discharged
Pregnancy testing	X (serum)	X (urine)			X (serum)	Females only
Physical examination	X	X (brief)	X (brief)	X (brief)	X	Day 3: 48 h post-dose Day 4: 72 h post-dose
Pharmacokinetics:						

Schedule of Assessments Part 1a (SAD)						
Assessments	**Screening**	**Treatment Period**			**Follow-up Visit**	**Comments**
	Days -28 to--2	**Day -1**	**Days 1 to 3 [a]**	**Day 4 [a]**	**(6±1 days post-dose)**	
Pharmacokinetic blood sampling			X [d)]	X [d)]	X [e]	**Cohort 1:** Day 1: Pre-dose and 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h and 12 h after start of dosing Day 2: 24 h, 30 h and 36 h post-dose Day 3: 48 h and 60 h post-dose. **Cohorts 2-3:** Day 1: Pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h and 12 h post-dose Day 2: 24 h, 30 h and 36 h post-dose **Cohorts 4:** Day 1: Pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose Day 2: 24 h, 30 h and 36 h post-dose Day 3: 48 h **Cohorts 5:** Day 1: Pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose Day 2: 24 h, 30 h and 36 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose

Schedule of Assessments Part 1a (SAD)						
Assessments	**Screening**	**Treatment Period**			**Follow-up Visit**	**Comments**
	Days -28 to--2	**Day -1**	**Days 1 to 3 [a]**	**Day 4 [a]**	**(6±1 days post-dose)**	
						Cohorts 6: Day 1: Pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h and 12 h post-dose Day 2: 24 h, 30 h and 36 h post-dose Day 3: 48 h post-dose Day 4: 72 h post-dose Follow-up Visit (single sample)
Exploratory Analyses:						
CCI [redacted]			X			6 h and 24 h post-dose
CCI [redacted]			X			Day 1: directly after dosing
CCI [redacted]			X			Day 1: only if healthy volunteer agrees by signing a separate informed consent form
CCI [redacted]		X [c, d)]	X [c, d)]			Day -1: single sample Day 1: 30 min, 1 h and 3 h post-dose
CCI [redacted]		X [c, d)]	X [c, d)]			Day -1: single sample Day 1: 30 min, 1 h and 3 h post-dose
CCI [redacted]		X			X	Day -1: single sample Follow-up Visit: single sample

BMI: Body mass index; dECG: Digital electrocardiogram; ECG: Electrocardiogram; CCI [redacted] SAE: Serious adverse event; CCI [redacted] TB: Tuberculosis

a) Healthy volunteers in cohort 1 will be discharged from the Clinical Unit after all samples have been collected and assessments have been performed on Day 4. Depending on the emerging data in cohort 1, the collection period may be extended to 96 hours post-dose, for cohort 2 onwards, in this case volunteers will only be discharged on Day 5.

b) The time-points for all procedures are relative to the start of the inhalation unless stated otherwise.
c) Only applicable to cohort 5 onwards.
d) Time-points may be updated based on emerging data.
e) For cohort 6 as indicated in the “Comments” column.

Table 6.2 Schedule of Assessments Part 1b (First IV Cohort)

Schedule of Assessments Part 1b (First IV Cohort)

Assessments	Screening [a]	Treatment Period			Follow-up Visit	Comments
	Days -28 to -2	Day -1	Days 1 to 2 [b]	Day 3 [b]	(6±1 days post-dose)	
Informed consent	X					Includes optional genetic consent
Inclusion/exclusion criteria	X	X				
Demographic data	X					
Medical history	X					
Drug, alcohol and cotinine screen	X	X				
Serology	X					
QuantiFERON® TB	X					
Follicle-stimulating hormone testing	X					Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:						
Admission		X				
Discharge				X		At least 60 h post-dose, may be extended up to 96 h post-dose depending on emerging data
Non-residential visit	X				X	
Investigational Medicinal Product Administration:						
AZD0449 IV administration [c]			Day 1 (0 hours)			60 min infusion duration
Safety and Tolerability:						
Adverse event questioning	Only SAEs	Only SAEs	X	X	X	
Spirometry	X	X	X	X	X	Day 1: Pre-dose and 1 h, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose
Pulse Oximetry	X	X	X	X	X	Day 1: Pre-dose and 30 min, 1 h, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose

Blood pressure, pulse and respiratory rate (supine) and body temperature	X	X	X	X	X	Day 1: Pre-dose and 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose
12-lead dECG			X	X		See Table 3.2-9 from the CSP
12-lead safety ECG	X	X	X	X	X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide, see Table 3.2-9 from the CSP
Telemetry		X	X			Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2)
Height, weight and BMI	X	X				
Clinical laboratory evaluations	X	X	X	X	X	Day 2: 24 h post-dose Day 3: 48 h post-dose All samples will be collected after a 10 h fasting period. If the assessment period is extended, Day 3 assessments will be performed on the day healthy volunteers are discharged
Pregnancy testing	X (serum)	X (urine)			X (serum)	Females only
Physical examination	X	X (brief)		X (brief)	X	Day 3: 48 h post-dose
Pharmacokinetics:						
Pharmacokinetic blood sampling			X	X		Day 1: Pre-dose and at 15, 30, 45 min after infusion start, **directly after the end of infusion (ca. 60 min),** 5, 10 and, 15 min after end of infusion, and 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h, and 16 h after infusion start Day 2: 24 h, 36 h and 48 h after infusion start
Optional pharmacogenetic sample			X			Day 1: Only if healthy volunteer agrees by signing a separate informed consent form and has not participated in Part 1a of the study

Exploratory Analyses:						
CCI [redacted]		X			X	Day -1: Single sample Follow-up Visit: Single sample

BMI: Body mass index; dECG: Digital electrocardiogram; ECG: Electrocardiogram; CCI [redacted] IV: Intravenous; SAE: Serious adverse event; CCI [redacted]; TB: Tuberculosis

a) Screening only applicable if healthy volunteer did not participate in Part 1a of the study.

b) Healthy volunteers will be discharged from the Clinical Unit after all samples have been collected and assessments have been performed on Day 3.

c) Two separate catheters/lines must be used for sampling and IV infusion to avoid sample contamination. The time-points for all procedures are relative to the start of the infusion.

Table 6.3 Schedule of Assessments Part 1b (Second IV Cohort)

Schedule of Assessments Part 1b (Second IV Cohort)

Assessments	Screening [a]	Treatment Period				Follow-up Visit	Comments
	Day -28 to Day -4 or -3	Day -3 to -2	Day -1	Days 1 to 2 [b]	Day 3 [b]	(6±1 days post-dose)	
Informed consent	X						Includes optional genetic consent
Inclusion/exclusion criteria	X		X				
Demographic data	X						
Medical history	X						
Drug, alcohol and cotinine screen	X	X					
Serology	X						
COVID-19 serology testing [d)]	X					X	
COVID-19 PCR testing [d)]	X	X					
QuantiFERON® TB	X						
Follicle-stimulating hormone testing	X						Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:							
Admission		X					
Discharge					X		At least 60 h post-dose, may be extended up to 96 h post-dose depending on emerging data
Non-residential visit	X					X	
Investigational Medicinal Product Administration:							
AZD0449 IV administration [c]				Day 1 (0 hours)			48 min infusion duration
Safety and Tolerability:							
Adverse event questioning	Only SAEs	Only SAEs	Only SAEs	X	X	X	

Spirometry	X		X	X	X		Day 1: Pre-dose and 1 h, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose
Pulse Oximetry	X		X	X	X	X	Day 1: Pre-dose and 30 min, 1 h, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose
Blood pressure, pulse and respiratory rate (supine) and body temperature	X		X	X	X	X	Day 1: Pre-dose and 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h post-dose Day 2: 24 h post-dose Day 3: 48 h post-dose
Body temperature		X					
12-lead dECG				X	X		See Table 3.2-9 from the CSP
12-lead safety ECG	X		X	X	X	X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide, see Table 3.2-9 from the CSP
Telemetry			X	X			Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2)
Height, weight and BMI	X		X			X	Height to be measured at screening only
Clinical laboratory evaluations	X	X		X	X	X	Day 2: 24 h post-dose Day 3: 48 h post-dose All samples will be collected after a 10 h fasting period. If the assessment period is extended, Day 3 assessments will be performed on the day volunteers are discharged
Pregnancy testing	X (serum)	X (urine)				X (serum)	Females only
Physical examination	X		X (brief)		X (brief)	X	Day 3: 48 h post-dose

Pharmacokinetics:							
Pharmacokinetic blood sampling				X	X		Day 1: Pre-dose and at 12, 24, 36 min after infusion start, **directly after the end of infusion (ca. 48 min),** 5, 10 and, 15 min after end of infusion, and 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 14 h, and 16 h after infusion start Day 2: 24 h and 36 h after infusion start Day 3: 48 h after infusion start
Optional pharmacogenetic sample				X			Day 1: Only if healthy volunteer agrees by signing a separate informed consent form and has not participated in Part 1a of the study
Exploratory Analyses:							
CCI [redacted]			X			X	Day -1: Single sample Follow-up Visit: Single sample

BMI: Body mass index; dECG: Digital electrocardiogram; ECG: Electrocardiogram; CCI [redacted] IV: Intravenous; PCR: Polymerase Chain Reaction; SAE: Serious adverse event; TB: Tuberculosis

a) Screening only applicable if volunteer did not participate in Part 1a of the study.

b) Healthy volunteers will be discharged from the Clinical Unit after all samples have been collected and assessments have been performed on Day 3.

c) Two separate catheters/lines must be used for sampling and IV infusion to avoid sample contamination. The time-points for all procedures are relative to the start of the infusion.

d) A sample for COVID-19 serology testing will be collected at screening and at the Follow-up visit. A swab sample for PCR will be collected at screening and prior to admission to the Clinical Unit; further samples for PCR and/or serology testing will be collected at the discretion of the Investigator. In the event of reduced COVID-19 sample analysis capacity sites may initiate residency visits from Day -3 if required. Ad hoc nasal and/or throat-swab specimen is to be collected for the identification of a suspected respiratory infection during any visit. Healthy volunteers who test positive for having active COVID-19 infection will be discontinued from the study and followed up until the final outcome of the AE.

Table 6.4 Schedule of Assessments Part 2a in patient with mild asthma

Schedule of Assessments Part 2a in patients with mild asthma

Assessments	Screening	Treatment Period					Follow-up	Comments
	Day -28 to Day -3	Day -2	Day -1	Day 1 and Day 2	Day 3 (start of once daily dosing) [a] to Day 12 (last dosing day) [a]	Day 13 to 15	Day 22±1 (10±1 days post-last dose)	
Informed consent	X							Includes optional genetic consent
Inclusion/exclusion criteria	X		X	X				
Demographic data	X							
Medical history	X							
Drug, alcohol and cotinine screen	X	X						
Serology	X							
QuantiFERON® TB	X							
Follicle-stimulating hormone testing	X							Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:								
Admission		X						
Discharge						X		Discharge on Day 14
Non-residential visit	X					X	X	Only Day 15 is non-residential
Investigational Medicinal Product Administration:								
Inhaler Nebulizer Training			X					
Randomization				X				Day 1
AZD0449/Placebo administration via Nebulizer [a]				X [b]	X [b]			First dose on Day 1, second dose on Day 3 (48 hours post-dose), then once daily dosing from Day 4 to Day 12

Safety and Tolerability:								
Adverse event questioning	Only SAEs	Only SAEs	Only SAEs	X	X	X	X	
Spirometry	X		X [c)]	X [c)]	X [c)]	X [c)]	X [c)]	Day -1: pre-dose, 6 h, 12 h (corresponding clock time) Day 1, Day 8 and Day 12: Pre-dose, 30 min, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3 to 7 and Day 9 to 11: pre-dose and 30 min post-dose Day 13: 24 h post-dose, Day 14: 47 h post-dose, Day 15: 71 h post-dose, and Day 22: 239 h post-dose
Pulse oximetry	X		X	X	X	X	X	Day -1: pre-dose, 3 h and 12 h post-dose (corresponding clock time) Day 1 and Day 3 to Day 12: Pre-dose, 1 h, 1.5 h, 3 h, 6 h, 12 h -post-dose Day 2: 24 h post-dose Day 13: 24 h post-dose Day 14: 47 h post-dose, Day 15: 71 h post-dose, and Day 22: 239 h post-dose
Blood pressure, pulse and respiratory rate (supine) and body temperature	X		X	X	X	X	X	Day 1 (first dose) and Day 12 (last dose):Pre-dose and 1 h, 2 h and 6 h post-dose Day 2: 24 h post-dose Days 3 to 11: pre-dose Day 13: 24 h post-dose
12-lead dECG				X	X	X		See Table 3.2-10 from the CSP
12-lead safety ECG	X		X	X	X	X	X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide see Table 3.2-10 from the CSP

Telemetry			X	X	X			Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2) Pre-dose (Day 12) to 24 h post-dose (Day 13)
Height, weight and BMI	X		X					
Clinical laboratory evaluations	X	X		X	X	X	X	Day 2: 24 h post-dose Day 3: pre-dose Day 13: 24 h post-dose All samples will be collected after a 10 h fasting period
Pregnancy testing	X (serum)	X (urine)					X (serum)	Females only
Physical examination	X		X	X (brief)	X (brief)	X (brief)	X	Day 1: pre-dose Day 2: 24 h after the first dose Day 6: pre-dose Day 10: pre-dose Day 13: 24 h post-dose
Pharmacokinetics:								
Pharmacokinetic blood sampling				X [c)]	X [c)]	X [c)]	X [c)]	Day 1 and 12: pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h [d)], and 12 h post-dose Day 2: 24 h, 30 h, and 36 h post-dose. Day 3 – Day 11: pre-dose Day 13: 24 h, 30 h, and 36 h post-last dose Day 14: 48 h post-last dose Day 15: 72 h post-last dose Day 22: 240 h post-last dose

Pharmacodynamics:								
Fractional exhaled nitric oxide	X		X [c)]	X [c)]	X [c)]	X [c)]	X [c)]	Single assessment at Screening Visit Day -1: (corresponding clock time) to pre-dose, 30 min and 2 h, 6 h and 12 h post-dose Days 1, 2, 3, 4, 6, 8, 10 and 12: Pre-dose (corresponding clock time), 30 min and 2 h, 6 h and 12 h post-dose Days 5, 7, 9 and 11: Pre-dose (corresponding clock time) and 2 h post-dose Day 13: 24 h and 26 h post-dose Day 14: 47 h and 50 h post-dose, Day 15: 71 h post-dose and Day 22: 239 h post-dose
Exploratory Analyses:								
CCI [redacted]	X		X		X	X		Single assessment at Screening Visit Day -1: pre-dose and 6 h post-dose (corresponding clock time) Days 8 and 12: pre-dose and 6 h post-dose Day 13: 24 h and 26 h post-dose
CCI [redacted]					X			Day 12: 2 h, 4 h, 8 h and 12 h post-last dose
CCI [redacted]			X			X	X	Day 13 and Day 22

CCI				X	X		X	Day 1 (pre-dose), Day 12 (pre-dose) and Day 22 single sampling
CCI				X				Day 1: only if patient agrees by signing a separate informed consent form
CCI				X	X			Day 1: Pre-dose Day 12 (last dosing day): Pre-dose

BMI: Body mass index; dECG: Digital electrocardiogram; ECG: Electrocardiogram; CCI SAE: Serious adverse event; TB: tuberculosis

a) The time-points for all procedures are relative to the start of the inhalation.
b) Single dose on Day 1 and once daily dosing on Day 3 – Day 12.
c) Time-points for assessments and sample collection may change based on emerging data. The Day 3 pre-dose blood sampling corresponds to 48 h post-Day 1 dose.
d) Only applicable to cohort 2 (Day 12 dosing only).

Table 6.5 Schedule of Assessments Part 2b in healthy volunteers

Table 3.2-5	Schedule of Assessments Part 2b in healthy volunteers

Assessments	Screening	Treatment Period					Follow-up	Comments
	Day -28 to Day -4 or -3	Day -3 to -2	Day -1	Day 1 and Day 2	Day 3 (start of once daily dosing) [a] to Day 12 (last dosing day) [a)]	Day 13 to 16	Day 17 to 27	
Informed consent	X							Includes optional genetic consent
Inclusion/exclusion criteria	X		X	X				
Demographic data	X							
Medical history	X							
Drug, alcohol and cotinine screen	X	X						
Serology	X							
COVID-19 serology testing [d)]	X						X	
COVID-19 PCR testing [d)]	X	X						
QuantiFERON® TB	X							
Follicle-stimulating hormone testing	X							Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:								
Admission		X						
Discharge						X		Discharge on Day 27.
Non-residential visit	X						X	
Investigational Medicinal Product Administration:								
Inhaler Nebulizer Training			X					
Randomization				X				Day 1
AZD0449/Placebo administration via Nebulizer [a)]				X [b)]	X [b)]			First dose on Day 1, second dose on Day 3 (48 hours post-dose), then once daily dosing from Day 4 to Day 12

Safety and Tolerability:								
Adverse event questioning	Only SAEs	Only SAEs	Only SAEs	X	X	X	X	
Spirometry	X		X [c)]	X [c)]	X [c)]	X [c)]	X [c)]	Day -1: pre-dose, 6 h, 12 h (corresponding clock time) Day 1, Day 8 and Day 12: Pre-dose 30 min, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3 to 7 and Day 9 to 11: pre-dose and 30 min post-dose Day 13: 24 h post-dose, Day 14: 47 h post-dose, Day 15: 71 h post-dose, Day 16: 95 h post-dose, Day 17: 120 h post-dose, Day 20: 192 h post-dose, Day 23: 264 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose
Pulse oximetry	X		X	X	X	X	X	Day 1 and Day 3 to Day 12: Pre-dose, 1 h, 1.5 h, 3 h, 6 h, 12 h -post-dose Day 2: 24 h post-dose Day 13: 24 h post-dose, Day 14: 48 h post-dose, Day 15: 72 h post-dose, Day 16: 96 h post-dose, Day 17: 120 h post-dose, Day 18: 144 h post-dose, Day 19: 168 h post-dose, Day 20: 192 h post-dose, Day 21: 216 h post-dose, Day 22: 240 h post-dose, Day 23: 264 h post-dose, Day 24: 288 h post-dose, Day 25: 312 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose

Blood pressure, pulse and respiratory rate (supine) and body temperature	X		X	X	X	X	X	Day 1 (first dose) and Day 12 (last dose): Pre-dose and 1 h, 2 h and 6 h post-dose Day 2: 24 h post-dose Days 3 to 11: Pre-dose Day 13: 24 h post-dose, Day 14: 48 h post-dose, Day 15: 72 h post-dose, Day 16: 96 h post-dose, Day 17: 120 h post-dose, Day 18: 144 h post-dose, Day 19: 168 h post-dose, Day 20: 192 h post-dose, Day 21: 216 h post-dose, Day 22: 240 h post-dose, Day 23: 264 h post-dose, Day 24: 288 h post-dose, Day 25: 312 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose
Body temperature		X				X		
12-lead dECG				X	X	X		See Table 3.2-10 from the CSP
12-lead safety ECG	X		X	X	X	X	X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide see Table 3.2-10 from the CSP
Telemetry			X	X	X	X		Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2) Pre-dose (Day 12) to 24 h post-dose (Day 13)
Height, weight and BMI	X		X				X	Height to be measured at screening only

Clinical laboratory evaluations	X	X		X	X	X	X	Day 2: 24 h post-dose Day 3: pre-dose Day 13: 24 h post-dose Day 27: 360 h post-last dose All samples will be collected after a 10 h fasting period
Pregnancy testing	X (serum)	X (urine)					X (serum)	Day 27 Females only
Physical examination	X		X	X (brief)	X (brief)	X (brief)	X	Day 1: pre-dose Day 2: 24 h after the first dose Day 6: pre-dose Day 10: pre-dose Day 14: 48 h post-dose, Day 17: 120 h post-dose, Day 20: 192 h post-dose, Day 23: 264 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose (full examination)

Pharmacokinetics:								
Pharmacokinetic blood sampling				X	X	X	X	Day 1 and 12: Pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h post-dose Day 2: 24 h, 30 h, and 36 h post-dose. Day 3 to Day 11: Pre-dose Day 13: 24 h, 30 h, and 36 h post-last dose Day 14: 48 h, 54 h, and 60 h post-last dose Day 15: 72 h, 78 h, and 84 h post-last dose Day 16: 96 h, 102 h, and 108 h post-last dose Day 17: 120 h post-last dose, Day 20: 192 h post-last dose, Day 23: 264 h post-last dose, Day 26: 336 h post-last dose, and Day 27: 360 h post-last dose
Exploratory Analyses:								
CCI [redacted]					X			Day 12: 2 h, 4 h, 8 h and 12 h post-last dose
CCI [redacted]				X	X			Day 1: pre-dose, Day 12: 3-8 h post-last dose

CCI [redacted]			X			X	X	Day 13 and Day 27
CCI [redacted]				X				Day 1: only if patient agrees by signing a separate informed consent form
CCI [redacted]				X		X		Day 1: Pre-dose Day 12 (last dosing day): Pre-dose

BMI: Body mass index; dECG: Digital electrocardiogram; ECG: Electrocardiogram; CCI [redacted] PCR: Polymerase Chain Reaction; SAE: Serious adverse event; TB: tuberculosis

a) The time-points for all procedures are relative to the start of the inhalation.

b) Single dose on Day 1 and once daily dosing on Day 3 – Day 12.

c) Time-points for assessments and sample collection may change based on emerging data. The Day 3 pre-dose blood sampling corresponds to 48 h post-Day 1 dose.

d) A sample for COVID-19 serology testing will be collected at screening and at the Follow-up visit. A swab sample for PCR will be collected at screening and prior to admission to the Clinical Unit; further samples for PCR and/or serology testing will be collected at the discretion of the Investigator. In the event of reduced COVID-19 sample analysis capacity sites may initiate residency visits from Day -3 if required. Ad hoc nasal and/or throat-swab specimen is to be collected for the identification of a suspected respiratory infection during any visit. Healthy volunteers who test positive for having active COVID-19 infection will be discontinued from the study and followed up until the final outcome of the AE.

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Informed consent	X								Includes optional genetic consent
Inclusion/exclusion criteria	X			X	X				
Demographic data	X								
Medical history	X								
Drug, alcohol and cotinine screen	X	X							
Serology	X								
COVID-19 serology testing [d)]	X							X	Day 27
COVID-19 PCR testing [d)]	X	X							
QuantiFERON® TB	X								
Follicle-stimulating hormone testing	X								Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:									
Admission		X							
Discharge							X		Discharge on Day 27

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Non-residential visit	X							X	Day 17 to Day 27 (If permitted by local relevant regulatory authorities and considered feasible and safe)
Investigational Medicinal Product									
DPI Training				X					
Randomization					X				Day 1
AZD0449/Placebo administration via DPI [a)]					X [b)]	X [b)]			First dose on Day 1, second dose on Day 3 (48 hours post-dose), then once daily dosing from Day 4 to Day 12

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Safety and Tolerability:									
Adverse event questioning	Only SAEs	Only SAEs	Only SAEs	Only SAEs	X	X	X	X	
Spirometry	X			X [c)]	X [c)]	X [c)]	X [c)]	X [c)]	Day -1: pre-dose, 6 h, 12 h (corresponding clock time) Day 1, Day 8 and Day 12: Pre-dose, 30 min, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3 to 7 and Day 9 to 11: pre-dose and 30 min post-dose Day 13: 24 h post-dose, Day 14: 47 h post-dose, Day 15: 71 h post-dose, Day 16: 95 h post-dose, Day 17: 120 h post-dose, Day 20: 192 h post-dose, Day 23: 264 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Pulse oximetry	X			X	X	X	X	X	Day -1: pre-dose, 3 h and 12 h post-dose (corresponding clock time) Day 1 and Day 3 to Day 12: Pre-dose, 1 h, 1.5 h, 3 h, 6 h, 12 h -post-dose Day 2: 24 h post-dose Days 13: 24 h post-dose, Day 14: 48 h post-dose, Day 15: 72 h post-dose, Day 16: 96 h post-dose, Day 17: 120 h post-dose, Day 18: 144 h post-dose, Day 19: 168 h post-dose, Day 20: 192 h post-dose, Day 21: 216 h post-dose, Day 22: 240 h post-dose, Day 23: 264 h post-dose, Day 24: 288 h post-dose, Day 25: 312 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Blood pressure, pulse and respiratory rate (supine)and body temperature	X			X	X	X	X	X	Day 1 (first dose) and Day 12 (last dose): Pre-dose and 1 h, 2 h and 6 h post-dose Day 2: 24 h post-dose Days 3 to 11: Pre-dose Day 13: 24 h post-dose, Day 14: 48 h post-dose, Day 15: 72 h post-dose, Day 16: 96 h post-dose, Day 17: 120 h post-dose, Day 18: 144 h post-dose, Day 19: 168 h post-dose, Day 20: 192 h post-dose, Day 21: 216 h post-dose, Day 22: 240 h post-dose, Day 23: 264 h post-dose, Day 24: 288 h post-dose, Day 25: 312 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose
Body temperature		X	X				X		
12-lead dECG					X	X	X		See Table 3.2-10 from the CSP
12-lead safety ECG	X			X	X	X	X	X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide, see Table 3.2-10 from the CSP

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Telemetry				X	X	X	X		Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2) Pre-dose (Day 12) to 24 h post-dose (Day 13)
Height, weight and BMI	X			X				X	Day 27 Height to be measured at screening only
Clinical laboratory evaluations	X	X			X	X	X	X	Day 2: 24 h post-dose Day 3: pre-dose Day 13: 24 h post-dose Day 27: 360 h post-last dose All samples will be collected after a 10 h fasting period
Pregnancy testing	X (serum)	X (urine)						X (serum)	Day 27 Females only

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Physical examination	X			X	X (brief)	X (brief)	X (brief)	X	Day 1: pre-dose Day 2: 24 h after the first dose Day 6: pre-dose Day 10: pre-dose Day 14: 48 h post-dose, Day 17: 120 h post-dose, Day 20: 192 h post-dose, Day 23: 264 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose (full examination)

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Pharmacokinetics:									

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Pharmacokinetic blood sampling					X [c)]	X [c)]	X [c)]	X [c)]	Days 1 and 12: pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h post-dose Day 2: 24 h, 30 h, and 36 h post-dose. Day 3 to Day 11: pre-dose Day 13: 24 h, 30 h, and 36 h post-last dose Day 14: 48 h, 54 h, and 60 h post-last dose Day 15: 72 h, 78 h, and 84 h post-last dose Day 16: 96 h, 102 h, and 108 h post-last dose Day 17: 120 h post-last dose, Day 20: 192 h post-last dose, Day 23: 264 h post-last dose, Day 26: 336 h post-last dose, and Day 27: 360 h post-last dose

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Pharmacodynamics:									

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
Fractional exhaled nitric oxide	X			X	X	X	X	X	Single assessment at Screening Visit Day -1: corresponding clock times to pre-dose, 30 min and 2 h, 6 h, and 12 h post-dose Days 1, 2, 3, 4, 6, 8, 10, and 12: Pre-dose (corresponding clock time), 30 min and 2 h, 6 h, and 12 h post-dose Days 5, 7, 9, and 11: Pre-dose (corresponding clock time) and 2 h post-dose Day 13: 23 h, 24.5 h, 26 h, 30 h, and 36 h post-last dose Day 14: 47 h, 48.5 h, 50 h, 54 h, and 60 h post-last dose Day 15: 71 h, 72.5 h, 74 h, 78 h, and 84 h post-last dose Day 16: 95 h, 96.5 h, 98 h, 102 h, and 108 h post-last dose Day 17, 20, 23, and 26: 5 measurements of FeNO (pre-dose, 30 min, 2 , 6 h, and

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
									12 h post-hypothetical dose Day 27: 2 measurements of FeNO (pre-dose and 2 h post-hypothetical dose)
Exploratory Analyses:									
CCI						X			Day 12: 2 h, 4 h, 8 h, and 12 h post-last dose
CCI				X			X	X	Day 13 and Day 27
CCI					X	X		X	Day 1 (pre-dose), Day 12 (pre-dose) and Day 27 single sampling
CCI				X		X			Day -1: single sample Day 12 (last dose): 30 min, 1 h and 3 h post-dose
CCI				X		X			Day -1 single sample Day 12 (last dose): 30 min, 1 h and 3 h post-dose
CCI					X				Directly after first dose

Table 6.7 Schedule of Assessments Part 3a in patients with mild asthma

Schedule of Assessments Part 3a in patients with mild asthma									
Assessments	**Screening**	**Treatment Period**					**Follow-up**		**Comments**
	Day -28 to Day -4	**Day -3**	**Day -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 216**	**Day 17 to Day 27**	
CCI [redacted]					X				Day 1: only if patient agrees by signing a separate ICF
CCI [redacted]					X	X			Day 1: pre-dose Day 12 (last dosing day): pre-dose

BMI: Body mass index; dECG: Digital electrocardiogram; DPI: Dry-powder inhaler; ECG: Electrocardiogram; CCI [redacted] ICF: Informed consent form; CCI [redacted] PCR: Polymerase Chain Reaction; SAE: Serious adverse event; CCI [redacted] TB: tuberculosis

a) The time-points for all procedures are relative to the start of the inhalation.

b) Single dose on Day 1 and once daily dosing on Day 3 – Day 12.

c) Time-points for assessments and sample collection may change based on emerging data. The Day 3 pre-dose blood sampling corresponds to 48 h post-Day 1 dose.

d) A sample for COVID-19 serology testing will be collected at screening and at the Follow-up visit. A swab sample for PCR will be collected at screening and prior to admission to the Clinical Unit; further samples for PCR and/or serology testing will be collected at the discretion of the Investigator. In the event of reduced COVID-19 sample analysis capacity sites may initiate residency visits from Day -3 if required. Ad hoc nasal and/or throat-swab specimen is to be collected for the identification of a suspected respiratory infection during any visit. Patients who test positive for having active COVID-19 infection will be discontinued from the study and followed up until the final outcome of the AE.

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Informed consent	X							Includes optional genetic consent
Inclusion/exclusion criteria	X		X	X				
Demographic data	X							
Medical history	X							
Drug, alcohol and cotinine screen	X	X						
Serology	X							
COVID-19 serology testing [d)]	X						X	Day 27
COVID-19 PCR testing [d)]	X	X						
QuantiFERON® TB	X							
Follicle-stimulating hormone testing	X							Post-menopausal females only (see CSP Section 5.2.3.2 for definition)
Study Residency:								
Admission		X						
Discharge						X		Discharge on Day 27.
Non-residential visit	X						X	Day 17 to Day 27 (If permitted by local relevant regulatory authorities and considered feasible and safe)

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Investigational Medicinal Product								
DPI Training			X					
Randomization				X				
AZD0449/Placebo administration via DPI [a)]				X [b)]	X [b)]			First dose on Day 1, second dose on Day 3 (48 hours post-dose), then once daily dosing from Day 4 to Day 12

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Safety and Tolerability:								
Adverse event questioning	Only SAEs	Only SAEs	Only SAEs	X	X	X	X	
Spirometry	X		X [c)]	X [c)]	X [c)]	X [c)]	X [d)]	Day -1: pre-dose, 6 h, 12 h (corresponding clock time) Day 1, Day 8 and Day 12: pre-dose, 30 min, 1.5 h, 3 h, 6 h and 12 h post-dose Day 2: 24 h post-dose Day 3 to 7 and Day 9 to 11: pre-dose and 30 min post-dose Day 13: 24 h post-dose, Day 14: 47 h post-dose, Day 15: 71 h post-dose, Day 16: 95 h post-dose, Day 17: 120 h post-dose, Day 20: 192 h post-dose, Day 23: 264 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Pulse oximetry	X		X	X	X	X	X	Day -1: pre-dose, 3 h and 12 h post-dose (corresponding clock time) Day 1 and Day 3 to Day 12: Pre-dose, 1 h, 1.5 h, 3 h, 6 h, 12 h -post-dose Day 2: 24 h post-dose Days 13: 24 h post-dose, Day 14: 48 h post-dose, Day 15: 72 h post-dose, Day 16: 96 h post-dose, Day 17: 120 h post-dose, Day 18: 144 h post-dose, Day 19: 168 h post-dose, Day 20: 192 h post-dose, Day 21: 216 h post-dose, Day 22: 240 h post-dose, Day 23: 264 h post-dose, Day 24: 288 h post-dose, Day 25: 312 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Blood pressure, pulse and respiratory rate (supine)and body temperature	X		X	X	X	X	X	Day 1 (first dose) and Day 12 (last dose): pre-dose and 1 h, 2 h and 6 h post-dose Day 2: 24 h post-dose Days 3 to 11: pre-Pre-dose Day 13: 24 h post-dose, Day 14: 48 h post-dose, Day 15: 72 h post-dose, Day 16: 96 h post-dose, Day 17: 120 h post-dose, Day 18: 144 h post-dose, Day 19: 168 h post-dose, Day 20: 192 h post-dose, Day 21: 216 h post-dose, Day 22: 240 h post-dose, Day 23: 264 h post-dose, Day 24: 288 h post-dose, Day 25: 312 h post-dose, Day 26: 336 h post-dose and Day 27: 360 h post-dose
Body temperature		X				X		
12-lead dECG				X	X	X		See Table 3.2-10 from the CSP
12-lead safety ECG	X		X	X	X	X	X	12-lead safety ECG will be collected at the start of each dECG extraction window when time-points coincide, see Table 3.2-10 from the CSP

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Telemetry			X	X	X	X		Day -1: at least 4 h Pre-dose (Day 1) to 24 h post-dose (Day 2) Pre-dose (Day 12) to 24 h post-dose (Day 13)
Height, weight and BMI	X		X				X	Day 27 Height to be measured at screening only
Clinical laboratory evaluations	X	X		X	X	X	X	Day 2: 24 h post-dose Day 3: pre-dose Day 13: 24 h post-dose Day 27: 360 h post-last dose All samples will be collected after a 10 h fasting period
Pregnancy testing	X (serum)	X (urine)					X (serum)	Day 27 Females only
Physical examination	X		X	X (brief)	X (brief)	X (brief)	X	Day 1: pre-dose Day 2: 24 h after the first dose Day 6: pre-dose Day 10: pre-dose Day 14: 48 h post-dose, Day 17: 120 h post-dose, Day 20: 192 h post-dose, Day 23: 264 h post-dose, Day 26: 336 h post-dose, and Day 27: 360 h post-dose (full examination)

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
Pharmacokinetics:								
Pharmacokinetic blood sampling				X [c)]	X [c)]	X [c), d)]	X [c)]	Days 1 and 12: pre-dose, as soon as possible after end of inhalation, 15 min after end of inhalation, and 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, and 12 h post-dose Day 2: 24 h, 30 h, and 36 h post-dose. Day 3 to Day 11: pre-dose Day 13: 24 h, 30 h, and 36 h post-last dose Day 14: 48 h, 54 h, and 60 h post-last dose Day 15: 72 h, 78 h, and 84 h post-last dose Day 16: 96 h, 102 h, and 108 h post-last dose Day 17: 120 h post-last dose, Day 20: 192 h post-last dose, Day 23: 264 h post-last dose, Day 26: 336 h post-last dose, and Day 27: 360 h post-last dose
Pharmacodynamics:								
Exploratory Analyses:								
CCI [redacted]					X			Day 12: 2 h, 4 h, 8 h, and 12 h post-last dose
CCI [redacted]			X			X	X	Day 13 and Day 27

Table 6.8 Schedule of Assessments Part 3b in healthy volunteers

Schedule of Assessments Part 3b in healthy volunteers								
Assessments	**Screening**	**Treatment Period**				**Follow-up**		**Comments**
	Day -28 to Day -4 or -3	**Day -3 to -2**	**Day -1**	**Day 1 and Day 2**	**Day 3 (second dosing day) to Day 12 (last dosing day)**	**Day 13 to 16**	**Day 17 to Day 27**	
CCI [redacted]				X				Directly after first dose
CCI [redacted]				X				Day 1: only if patient agrees by signing a separate ICF
CCI [redacted]				X	X			Day 1: Pre-dose Day 12 (last dosing day): Pre-dose

BMI: Body mass index; dECG: Digital electrocardiogram; ECG: Electrocardiogram; CCI [redacted] PCR: Polymerase Chain Reaction; SAE: Serious adverse event; TB: tuberculosis

a) The time-points for all procedures are relative to the start of the inhalation.

b) Single dose on Day 1 and once daily dosing on Day 3 – Day 12.

c) Time-points for assessments and sample collection may change based on emerging data. The Day 3 pre-dose blood sampling corresponds to 48 h post-Day 1 dose.

d) A sample for COVID-19 serology testing will be collected at screening and at the Follow-up visit. A swab sample for PCR will be collected at screening and prior to admission to the Clinical Unit; further samples for PCR and/or serology testing will be collected at the discretion of the Investigator. In the event of reduced COVID-19 sample analysis capacity sites may initiate residency visits from Day -3 if required. Ad hoc nasal and/or throat-swab specimen is to be collected for the identification of a suspected respiratory infection during any visit. Healthy volunteers who test positive for having active COVID-19 infection will be discontinued from the study and followed up until the final outcome of the AE.

Table 6.9 Time Schedule for Digital Electrocardiogram Part 1a (SAD)

Study Days	ECG Number	Time-point	Start Time hour:min [a), b)]	Dose	Stop Time	dECG cont. [c), d), e)]	Other [f)]
1			-01:30		-01:00		Apply the electrodes [d)]
1			-00:40		-00:30		Rest in bed
1	1	Pre-dose	-00:30	Pre-dose	-00:20	10 minutes	
1			-00:20		-00:05		Toilet use recommended
1			00:00	Administration of AZD0449/placebo			
1	2	1 h	00:55		01:00	5 minutes [e)]	
1	3[g)]	2 h	01:55		02:00	5 minutes [e)]	
1	4	3 h	02:55		03:00	5 minutes [e)]	
1	5	4 h	03:55		04:00	5 minutes [e)]	
1	6 [h)]	5 h	04:55		05:00	5 minutes [e)]	
1	7	6 h	05:55		06:00	5 minutes [e)]	
1	8	8 h	07:55		08:00	5 minutes [e)]	
1	9 [h)]	10 h	09:55		10:00	5 minutes [e)]	
1	10	12 h	11:55		12:00	5 minutes [e)]	
2	11	24 h	23:55		24:00	5 minutes [e)]	
2	12	36 h	35:55		36:00	5 minutes [e)]	
3	13	48 h	47:55		48:00	5 minutes [e)]	
3	14 [h)]	60 h	59:55		60:00	5 minutes [e)]	

ECG: Electrocardiogram; dECG: Digital ECG; PK: Pharmacokinetics

a) Time-points for dECG may be adjusted according to emerging PK data.
b) Times are approximate as dECG and safety ECGs need to be completed before blood sampling.
c) The healthy volunteer must be in the same supine body position (max. 30 degrees flexion in the hip) at each time-point and at all visits. Healthy volunteer's feet should not contact the footboard of the bed.
d) Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before first recording.
e) Healthy volunteer must rest in bed for at least 10 minutes before each ECG time-point.
f) Safety ECG will be collected at the start of each dECG extraction window.
g) For cohorts 1 to 4 only.

h) For cohorts 1 to 3 only.

Table 6.10 Time Schedule for Digital Electrocardiogram Part 1b (IV Cohorts)

Study Days	ECG Number	Time-point	Start Time hour:min[a) b), c)]	Dose	Stop Time	dECG cont. [c), d) e)]	Other [f)]
1			-01:30		-01:00		Apply the electrodes [d)]
1			-00:40		-00:30		Rest in bed
1	1	Pre-dose	-00:30	Pre-dose	-00:20	10 minutes	
1			-00:20		-00:05		Toilet use recommended
1			00:00	Infusion start			
1	2	5 min	00:05		00:10	5 minutes [e)]	After infusion start
1	3	30 min	00:25		00:30	5 minutes [e)]	
1	4	48 min [h)]	00:43		00:48	5 minutes [e)]	
1	5	1 h [g)]	00:55		01:00	5 minutes [e)]	
1	6	1.5 h	01:25		01:30	5 minutes [e)]	
1	7	2 h	01:55		02:00	5 minutes [e)]	
1	8	3 h	02:55		03:00	5 minutes [e)]	
1	9	4 h	03:55		04:00	5 minutes [e)]	
1	10	5 h	04:55		05:00	5 minutes [e)]	
1	11	6 h	05:55		06:00	5 minutes [e)]	
1	12	8 h	07:55		08:00	5 minutes [e)]	
1	13	10 h	09:55		10:00	5 minutes [e)]	
1	14	12 h	11:55		12:00	5 minutes [e)]	
2	15	24 h	23:55		24:00	5 minutes [e)]	
2	16	36 h	35:55		36:00	5 minutes [e)]	
3	17	48 h	47:55		48:00	5 minutes [e)]	

ECG: Electrocardiogram; dECG: Digital ECG; PK: Pharmacokinetics

a) Time-points for dECG may be adjusted according to emerging PK data.

b) Times are approximate as dECG and safety ECGs need to be completed before blood sampling.

c) The healthy volunteer must be in the same supine body position (max. 30 degrees flexion in the hip) at each timepoint and at all visits. Healthy volunteer's feet should not contact the footboard of the bed.
d) Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before first recording.
e) Healthy volunteer must rest in bed for at least 10 minutes before each ECG timepoint.
f) Safety ECG will be collected at the start of each dECG extraction window.
g) For cohort 1 only.
h) For cohort 2 only.

Table 6.11 Time Schedule for Digital Electrocardiogram Part 2a/b and Part 3a/b

Study Days	ECG Number		Time-point	Start Time hour:min [a),b)]	Dose	Stop Time	dECG cont. [c),d),e)]	Other [f)]
1, 12				-01:30	Pre-dose	-01:00		Apply the electrodes [d)]
1, 12				-00:40		-00:30		Rest in bed
1, 12	1	11	Pre-dose	-00:30		-00:20	10 minutes	
1, 12				-00:20		-00:05		Toilet use recommended
1, 12				00:00	Administration of AZD0449/placebo			
1, 12	2	12	0.5 h [g)]	00:25		00:30	5 minutes [e)]	
1, 12	3	13	1 h	00:55		01:00	5 minutes [e)]	
1, 12	4	14	3 h	02:55		03:00	5 minutes [e)]	
1, 12	5	15	4 h	03:55		04:00	5 minutes [e)]	
1, 12	6	16	6 h	05:55		06:00	5 minutes [e)]	
1, 12	7	17	8 h	07:55		08:00	5 minutes [e)]	
1, 12	8	18	12 h	11:55		12:00	5 minutes [e)]	
2, 13	9	19	24 h	23:55		24:00	5 minutes [e)]	
2, 13	10	20	36 h	35:55		36:00	5 minutes [e)]	
14		21	48 h	47:55		48:00	5 minutes [e)]	

ECG: Electrocardiogram; dECG: Digital ECG; PK: Pharmacokinetics

a) Time-points for dECG may be adjusted according to emerging PK data.
b) Times are approximate as dECG and safety ECGs need to be completed before blood sampling.
c) The patient must be in the same supine body position (max. 30 degrees flexion in the hip) at each time-point and at all visits. Patient's feet should not contact the footboard of the bed.
d) Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before first recording.
e) Patient must rest in bed for at least 10 minutes before each ECG time-point.
f) Safety ECG will be conducted at the start of each dECG extraction window.
g) Part 3a/b only.

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