Clinical Study Protocol	
Study Intervention	AZD1402
Study Code	D2912C00003
Version	8.0
Date	24 Mar 2023

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

Sponsor Name:

Legal Registered Address: AstraZeneca AB, SE-15185 Södertälje, Sweden

Regulatory Agency Identifier Number

EudraCT Number: 2020-002828-37

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

Protocol Number: D2912C00003

Amendment Number: 7

Study Intervention: AZD1402

Study Phase: IIa

Short Title: Efficacy and Safety of Inhaled AZD1402 administered Twice Daily for Four Weeks in Adults with Asthma on Medium-to-High Dose Inhaled Corticosteroids

Acronym: APATURA

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 7	24 Mar 2023
Amendment 6	03 Aug 2022
Amendment 5	04 Mar 2022
Amendment 4	13-Jan-2022
Amendment 3	09-Jun-2021
Amendment 2	10-Mar-2021
Amendment 1	23-Nov-2020
Original Protocol	20-Oct-2020

Amendment 7 (24 Mar 2023)

The Clinical Study Protocol (CSP) version 7.0, 03 Aug 2022 has been amended to optimize the selection of the participant population to be included in Part 2 of the study. The CSP changes included the update of period of required stable control by maintenance control medications, removal of inclusion criterion that participant should have had at least one severe asthma exacerbation in the 3 years prior to Visit 1, update of Part 2-specific inclusion and randomisation criteria to allow patients with FEV_1 range from 40% to 85% (instead of patients with FEV_1 range 50% to 85%) and C-reactive protein of < 10 mg/ml (instead of < 5 mg/ml) be included, update of Part 2-specific criterion related to minimum ePRO compliance (70% completion instead of 80%) to reduce impact of participant burden and align with asthma controller compliance requirements, update of exclusion criteria related to COVID-19 and TB infections. Other CSP changes included the update of the number of participants included in Part 2 (to 165 from 180), update of follow-up anti-drug antibody (ADA) sample collection, and amendment of the interim analysis text to allow flexibility on timing. Additional requirements for European Union Clinical Trial Regulation (EU-CTR) have been included. Furthermore, some study procedures have been clarified and inconsistencies in the CSP text have been corrected.

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis Section 1.2 Figure 1	Follow-up ADA sample collection timing updated to 'approximately 2 years after randomisation' from '2 years after randomisation'	To account for logistical considerations in recall of participants and timing of sample collection	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 Table 1			
Section 1.1 Synopsis Section 4.1.1 Figure 3 Section 4.1.2 Section 9.5	Main purpose of interim analysis changed to estimate the variability for a sample-size re-estimation or perform futility analysis in Part 2. The timing of the interim analysis in Part 2 was corrected	Added flexibility on timing of interim analysis and estimated variability enable an informative decision on whether to revise the sample size in Part 2	Non-substantial
Section 1.1 Synopsis Section 4.1.1 Figure 3 Section 4.1.2 Section 9.2	Planned number of participants in Part 2 updated to 165 from 180. Number of participants randomised into the [redacted] mg arm corrected to 5 from 20	To reflect number of participants randomised prior to stopping randomisation into the [redacted] mg arm (reduced to 5 from 20)	Non-substantial
Section 1.1 Synopsis Section 4.1.2 Section 5.1.2	Stability of ICS-LABA dose requirement prior to Visit 1 updated from 3 months to 4 weeks	To take into account existing duration of screening and run-in period prior to randomisation	Substantial
Section 1.1 Synopsis Section 4.1.2 Section 5.1.2	Stability of additional maintenance controller medications prior to Visit 1 updated from 3 months to 4 weeks	To take into account existing duration of screening and run-in period prior to randomisation	Substantial
Section 1.3 Table 2	Footnote clarified to include information about serum pregnancy test in case of positive result of urine pregnancy test in Part 2	For verification of pregnancy status (leading to permanent discontinuation of study intervention in case of positive result)	Non-substantial
Section 4.1.2 Section 5.1.2	Removal of inclusion criterion that participant should have at least one severe asthma exacerbation in the 3 years prior to Visit 1	Amended to optimise selection of the participant population allowing participants without severe asthma exacerbations to be included in Part 2	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 4.1.2 Section 5.1.2 Section 5.1.4	Part 2-specific inclusion and randomisation criteria updated to have FEV_1 range from 40% to 85%. Amended throughout the protocol as applicable	Amended to optimise selection of the participant population using broader FEV_1 range inclusion criteria	Substantial
Section 4.4	Clarified definition of the end of study according to European Union and Food and Drug Administration requirements.	For consistency and alignment in terms of posting study results	Non-substantial
Section 5.1.4	Part 2-specific randomisation criterion updated minimum compliance with ePRO completion to 70%	Amended to optimize selection of the participant population using less stricter compliance randomisation criteria	Substantial
Section 5.1.4	Part 2-specific randomisation criterion regarding level of C-reactive protein at Visit 2 updated to < 10 mg/L from < 5 mg/L	Amended to optimize selection of the participant population using broader range for C-reactive protein	Substantial
Section 5.2 Section 5.4	Update of exclusion criteria on participants with history of severe COVID-19 and further clarification of diagnosis of COVID-19 and removal of text related to rescreening participants diagnosed with SARS-COV-2	Amended to perform diagnostics as per local guidelines and as clinically indicated	Substantial
Section 5.2 Section 1.3 Table 2	Update of exclusion criteria on participants with active TB and footnote in Schedule of Activities for Part 2 aligned	Amended to perform diagnostics as per local guidelines and as clinically indicated	Substantial
Section 5.3.4	Additional restriction added to exclude MART	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	regime for the duration of the study		
Section 6.4.2	Updated e-Diary compliance description	Updated to align with updated inclusion criteria	Substantial
Section 8.2.4	Clarified requirements for results of Hepatitis C – Virus Antibody and PCR tests for participants that may be enrolled	For consistency and alignment with exclusion criterion 12	Non-substantial
Section 8.3.10.2	Updated information about paternal exposure in line with inclusion criterion	To correct inconsistencies in the protocol	Non-substantial
Section 8.3.11	Added Drug Abuse and Drug Misuse definition	Update required due to 'CT-3' Regulation and corporate safety CAPA	Non-substantial
Section 9.4.4.2	Presentation of immunogenicity AEs results changed from graphical to tabular	For clarification	Non-substantial
Appendix A1	Added sub-section "Regulatory Reporting Requirements for Serious Breaches"	Update required to comply with regulatory requirement (eg, EU-CTR) and global company requirement	Non-substantial
Appendix A6	Updated information about dissemination of clinical study data	Update required to comply with EU-CTR	Non-substantial
Appendix A7	Updated information about retention timelines of records and documents to 25 years after study archiving	Update required to comply with EU-CTR and global company requirement	Non-substantial
Appendix B4	Updated to include latest template wording on Medication error, drug abuse, and drug misuse	Update required due to 'CT-3' Regulation and corporate safety CAPA	Non-substantial
Appendix K	Changes from previous amendment moved to appendix	Update as per template requirements	Non substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

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

Short Title: Efficacy and Safety of Inhaled AZD1402 administered Twice Daily for Four Weeks in Adults with Asthma on Medium-to-High Dose Inhaled Corticosteroids

Rationale:

Asthma is a chronic, complex, and heterogeneous respiratory disease characterised by a range of pathogenic features including pulmonary inflammation, mucus hypersecretion, variable airway obstruction, and airway remodelling. Symptoms and airway obstruction can resolve in response to therapy or spontaneously, but participants remain at risk of severe worsening of their asthma (exacerbations). These asthma exacerbations can be life-threatening, can significantly impact the participant's quality of life, and result in significant healthcare costs.

International treatment guidelines for asthma recommend inhaled corticosteroids (ICS) as first line therapy. For individuals who are symptomatic on medium dose ICS monotherapy, step-up therapy with long-acting beta agonists (LABAs) is the recommended next treatment option followed by other controller therapies including leukotriene receptor antagonists, theophylline, and oral corticosteroids (OCS). 'Biologic agents' (eg, omalizumab and benralizumab) that inhibit specific molecular targets such as immunoglobulin E (IgE) or T helper cell type 2 (Th2) cytokines and their respective receptors are reserved for those with severe uncontrolled asthma. For most asthma participants, a treatment regime of a controller and bronchodilator therapy provides adequate long-term control. Inhaled corticosteroids are considered the "gold standard" in controlling asthma symptoms and LABAs are the most effective bronchodilators currently available. These agents are often given in combination as research has demonstrated that combination therapy of an ICS with an inhaled LABA provides better asthma control than high doses of ICS alone. Although the majority of participants respond to therapy, it is estimated that 5% to 10% of the population with asthma has symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. For those moderate/severe asthma participants that remain uncontrolled on currently approved inhaled or oral treatments there is a clear unmet need for new therapies before introducing systemic biologic treatment. Inhalation as opposed to systemic and subcutaneous administration of biologics, could offer several potential advantages. Inhaled drugs are advantageous as the drug delivery is localised to the lung (target organ) which may allow for a lower dose than needed with systemic delivery. Inhalation is also non-invasive,

and thus offers advantages in terms of ease of use. Current research is focusing on the different pathological mechanisms or endotypes of severe asthma and it is anticipated that this will lead to the development of effective therapies for these subsets of asthma patients.

AZD1402 is derived from human tear lipocalin (Tlc) and is a potent and selective antagonist of interleukin (IL)-4Rα, which antagonises the pro-inflammatory actions of IL-4 and IL-13. AZD1402 is presented as an inhalation powder and belongs to a new class of therapeutics, Anticalin® proteins, which are modified lipocalins. AZD1402 is being developed as an inhaled IL-4Rα antagonist controller therapy for the treatment of moderate to severe persistent asthma in participants who are not adequately controlled on standard of care therapies. The current study aims to assess the efficacy and safety of inhaled AZD1402 administered via dry power inhaler (DPI) CCI for 4 weeks in adults with asthma on medium-to-high dose ICS in a 2-part randomised, double-blind, placebo-controlled, and multi-centre study.

Objectives and Endpoints

Part 1	
Objectives	**Outcome Measure**
Primary	
• To evaluate the safety and tolerability of AZD1402 compared to placebo at different dose levels in adults with asthma controlled on medium dose ICS-LABA	**Primary safety endpoint:** • Adverse events / AESIs / SAEs with a particular focus on infection, eosinophilia, and hypersensitivity-like events • Vital signs • Changes in clinical chemistry, haematology, and coagulation parameters • Immuno-biomarkers (including but not limited to cytokines, CRP, immunoglobulins including IgE) • ECGs • FEV_1 • FeNO (in-clinic)
Secondary	
• To investigate the PK profile and immunogenicity of AZD1402, and associated effects on safety	• PK parameters (full profile in all participants) • ADAs
Exploratory	
• CCI	• Change from baseline in FeNO at Day 28 and average over the Treatment Period • CCI

Part 1	
Objectives	**Outcome Measure**
• To assess the effect of AZD1402 compared to placebo on cough by a VAS in adults with asthma controlled on medium dose ICS-LABA	• Change from baseline average in cough VAS over the Treatment Period
• CCI [redacted]	• CCI [redacted] • CCI [redacted]
• CCI [redacted]	• CCI [redacted] • CCI [redacted]
• CCI [redacted]	• CCI [redacted] • CCI [redacted]

Abbreviations: CCI [redacted] ADAs = anti-drug antibodies; AESI = adverse event of special interest; CSR = clinical study report; CRP = C-reactive protein; ECG = electrocardiogram; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; CCI [redacted] ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting beta agonist; CCI [redacted] PK = pharmacokinetics; SAEs = serious adverse events; VAS = Visual Analogue Scale

Part 2	
Objectives	**Outcome Measure**
Primary	
• To investigate the efficacy of inhaled AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	**Primary efficacy endpoint:** • Change from baseline in pre-bronchodilator FEV_1 at Week 4
Secondary	
• To further investigate the efficacy of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	• Change from baseline in pre-bronchodilator FEV_1 average over the 4-week Treatment Period • Change from baseline in ACQ-6 at Week 4 and average over the Treatment Period • Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 4 • Change from baseline in average morning PEF over the Treatment Period • Change from baseline in average evening PEF over the Treatment Period

Part 2	
Objectives	**Outcome Measure**
	• Change from baseline in daily average asthma symptom score (AM/PM) over the Treatment Period
• To investigate the effect of AZD1402 compared to placebo on airway inflammation in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	• Change from baseline in FeNO (in-clinic) at Week 4 and average over the Treatment Period
• To investigate the PK profile and immunogenicity of AZD1402, and associated effects on safety	• PK parameters (sparse in all, full profile in a subset of participants in each treatment arm) • ADAs
• To evaluate the safety and tolerability of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	• Adverse events / AESIs / SAEs with a particular focus on infection, eosinophilia, and hypersensitivity-like events • Vital signs • Changes in clinical chemistry, haematology, and coagulation parameters • Immuno-biomarkers (including but not limited to cytokines, CRP, immunoglobulins including IgE) • ECGs • FEV_1 • FeNO (in-clinic)
Exploratory	
• CCI	• CCI • CCI • CCI • CCI • CCI • CCI • Change from baseline in FeNO (in-clinic)
• CCI	• CCI CCI
• CCI	• CCI • CCI
• CCI	• CCI CCI

Part 2	
Objectives	**Outcome Measure**
CCI	

Abbreviations: ACQ-6 = Asthma Control Questionnaire-6; AESIs = adverse events of special interest; ADAs = anti-drug antibodies; AM = before noon (antemeridiem); CRP = C-reactive protein; CSR = clinical study report; ECG = electrocardiogram; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; CCI ; ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting beta agonist; CCI ; PEF = peak expiratory flow; PK = pharmacokinetics; PM = after noon (post meridiem); SAEs = serious adverse events

Overall Design

This is a randomised, placebo-controlled, double-blinded, multi-centre, 2-part study to assess the efficacy and safety of inhaled AZD1402. Part 1 will be performed in a Lead-in Cohort for each dose level to evaluate the safety and pharmacokinetics (PK) in a population with asthma controlled on medium dose ICS-LABA before progressing to at-home dosing in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA in Part 2. Part 2 will be initiated following evaluation of safety and PK in Part 1a. The study intervention in both parts of the study will be administered CCI using the CCI DPI for a period of 4 weeks.

A Lead-in Dose Progression and Escalation Cohort approach with 3 dose levels has been selected to confirm Phase I data dose-response observations and further evaluate safety and PK in adults with asthma controlled on medium dose ICS. The Part 1a safety cohort will be completed before progressing to at-home dosing in adults with asthma uncontrolled on medium-to-high dose ICS-LABA in Part 2.

This study will be conducted in approximately 8-10 countries. The entire study period for each participant in both Parts 1 and 2, is approximately 3.5 months; a 2-week Screening Period, a 4-week Run-in Period, 4 weeks of Treatment Period, and 4 weeks of Follow-up Period.

Part 1

Part 1 of the study will be randomised, double-blind, placebo-controlled, and conducted in parallel for the 2 CCI dose levels (Part 1a) followed by an unblinded safety review and escalation to the CCI dose (Part 1b) dependent on the outcome of the safety review. Data evaluated in the safety review will be unblinded; however, blinding will be maintained for participants and Investigators. The total sample size for Part 1 is estimated to be 45 participants.

The target population is adults with asthma (age 18 to 75 years, inclusive) who are adequately controlled on a stable medium dose ICS-LABA and additional rescue medication as needed, Asthma Control Questionnaire-6 (ACQ-6) score ≤ 1.0 and pre-bronchodilator forced

expiratory volume in one second (FEV_1) ≥ 70%, and with no exacerbation requiring systemic treatment or hospitalisation/emergency department visit for asthma during the 12 months prior to study start.

Part 1a will consist of 30 participants who will be randomised 1:1:1 to receive 1 of the 2 CCI AZD1402 DPI doses (CCI mg) or placebo in parallel. Part 1b will consist of 15 participants who will be randomised 2:1 to receive the CCI AZD1402 DPI dose (CCI mg) or placebo. Due to logistical reasons, the randomisation in Part 1 will be stratified by site in Australia and Germany.

Part 1a Lead-in Cohort

- AZD1402 inhalation CCI mg CCI
- AZD1402 inhalation CCI mg CCI
- Placebo inhalation CCI

Part 1b Lead-in Cohort

- AZD1402 inhalation CCI mg CCI
- Placebo inhalation CCI

Part 2

Part 2 will be randomised, double-blind, placebo-controlled and will include approximately 165 participants to evaluate 2 inhaled dose levels (CCI mg and CCI mg) of AZD1402 against placebo. Approximately 5 participants will be randomised to CCI mg and 80 participants per arm will be randomised to CCI mg and placebo, respectively. The number of subjects enrolled in the CCI mg dose will depend on the enrolment rate and the randomisation ratio will change during the study. Patients will be randomised 2:1 (active to placebo) whilst the CCI mg arm is ongoing. Once the CCI mg has stopped recruiting and randomisation continues in the CCI mg and placebo arms, the randomisation ratio will be 1:1 (active to placebo). Adult participants (age 18 to 75 years, inclusive) with physician-diagnosed uncontrolled asthma treated with medium-to-high dose ICS (total daily dose > 400µg of budesonide dry powder formulation or equivalent) with LABA, as maintenance treatment, for at least 6 months prior to Visit 1 will be included. ICS-LABA and any additional asthma maintenance controller medications (eg, leukotriene receptor inhibitors, theophylline, long-acting muscarinic antagonist [LAMA], and chromones) must be stable for at least 4 weeks prior to Visit 1.

Apart from the scheduled clinic visits, the 4 weeks of dosing in Part 2 of the study will be at home. Part 2 will be started after the unblinded safety review for Part 1a. Part 2 will include:

- AZD1402 inhalation CCI mg CCI

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

Participants in both parts of the study will receive a handheld e-Diary device which they are required to complete twice daily during the entire duration of the study.

Disclosure Statement: For Part 2 this is a parallel group treatment study with 3 arms that is participant, Investigator, and Sponsor blinded.

Number of Participants:

Approximately 45 participants will be randomised in Part 1 of the study and approximately 165 participants will be randomised in Part 2 of the study.

Intervention Groups and Duration:

Both parts of the study will have a Screening Period of 14 days. The Run-in, Treatment Period, and Follow-up Periods are 28 days each. In Part 1 only, participants with a positive ADA sample at the final Follow-up Visit, will also have an anti-drug antibody (ADA) sample taken up to approximately 2 years after randomisation.

Data Monitoring Committees:

An unblinded Safety Review Committee (SRC), including the Sponsor study team will review PK and unblinded safety data following the completion of Part 1a before progressing to Part 1b/2, and following completion of Part 1b. An unscheduled SRC meeting may also be held in the event of any safety or tolerability events requiring further review that may impact continuation of a cohort or the study, including unblinding data as required.

A Data Safety Monitoring Board (DSMB) will oversee Part 2 of the study and review the unblinded interim outputs. In addition to a full DSMB periodic review of safety data, the committee can meet on an ad hoc basis.

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

Details of the composition of the each of these committees, frequency of meetings, and remit can be found in the respective charters.

Statistical Methods

No statistical hypotheses will be tested for in Part 1 (Lead-in Cohort) of this study.

The null hypotheses for the primary analysis in Part 2 (Main Cohort) are that there is no difference in the change from baseline at Week 4 in FEV_1 in AZD1402 treated participants

compared to placebo-treated participants.

Sample Size:

In Part 1 (Lead-in Cohort), approximately 45 participants will be randomised. Part 1a will consist of 30 randomised participants and Part 1b will consist of 15 randomised participants. The sample size for Part 1 (Lead-in Cohort) is not based on any sample size calculation, but was chosen to obtain reasonable evidence of safety and tolerability without exposing undue number of participants to the study intervention.

In Part 2 (Main Cohort), 73 evaluable participants per treatment arm ([CCI] mg and placebo) will provide [CCI]% power using a 1-sided test and [CCI]% significance level to detect a difference of 175 mL in FEV_1 versus placebo. Assuming a dropout rate of [CCI]%, approximately [CCI] evaluable participants per arm are needed. Due to the restricted recruitment into the [CCI] mg dose arm the precision of inference in terms of statistical power will be less than [CCI]% for the comparisons [CCI] mg versus placebo. A participant will be considered evaluable if he/she has baseline and Week 4 FEV_1 results available. Part 2 will include approximately 165 participants (5, 80 and 80 in the [CCI] mg, [CCI] mg and placebo arms, respectively).

General Statistical Considerations:

Continuous data will be summarised using descriptive statistics. For log-transformed data geometric mean and geometric coefficient of variation will also be presented. For PK data, geometric ± standard deviation (SD) will also be presented in addition to geometric mean and geometric coefficient of variation. Frequencies and percentages will be used for summarising categorical (discrete) data.

Confidence intervals will generally be 2-sided with 95% confidence level, and p-values will be one-sided, unless otherwise indicated.

Unless otherwise stated, summaries will be presented by Part and treatment. The treatment comparisons of interest are the different doses of AZD1402 versus placebo. No formal comparisons between the different AZD1402 doses will be conducted.

The analysis of all efficacy variables (Part 2) will be performed on the full analysis set (FAS). Mixed model repeated measures analysis (MMRM) will be used for primary efficacy endpoint, within-participant correlation will be modelled using the unstructured covariance matrix and Kenward-Roger approximation will be used to estimate the degrees of freedom.

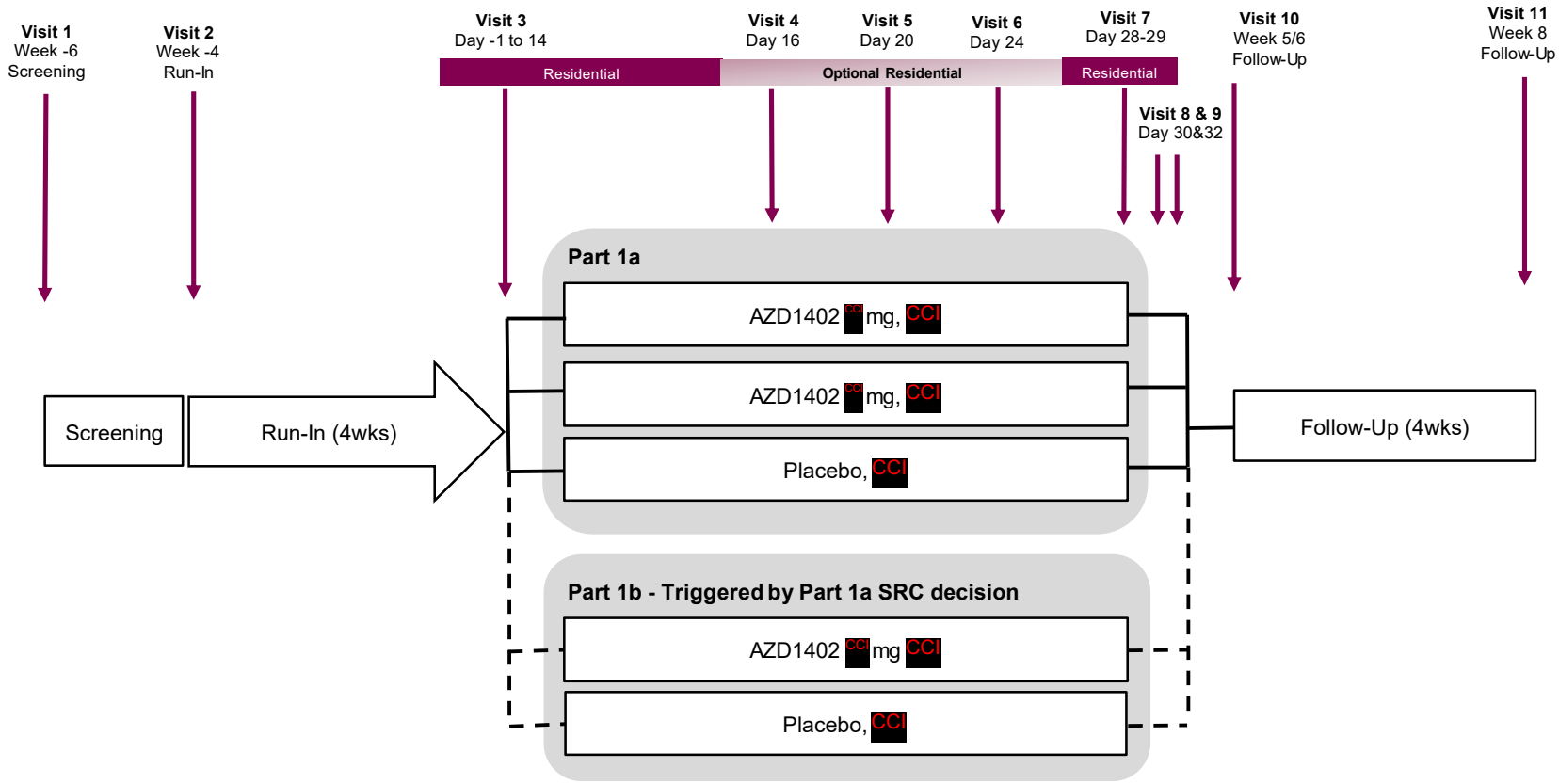
Safety analysis will be performed using the safety set (SS). Safety data will be presented descriptively unless otherwise specified. Adverse events (AEs) will be presented separate for each Part by treatment, system organ class and/or preferred term covering number and percentage of participants reporting at least one event and number of events where

appropriate.

An interim analysis of the primary endpoint (FEV_1) may be performed. The main objective of this analysis is to estimate the variability for a sample-size re-estimation or perform a futility analysis. The timing of the interim analysis is to be determined such that the estimated variability enables an informative decision on whether to revise the sample size. Decision criteria will be pre-specified in an interim analysis plan (charter).

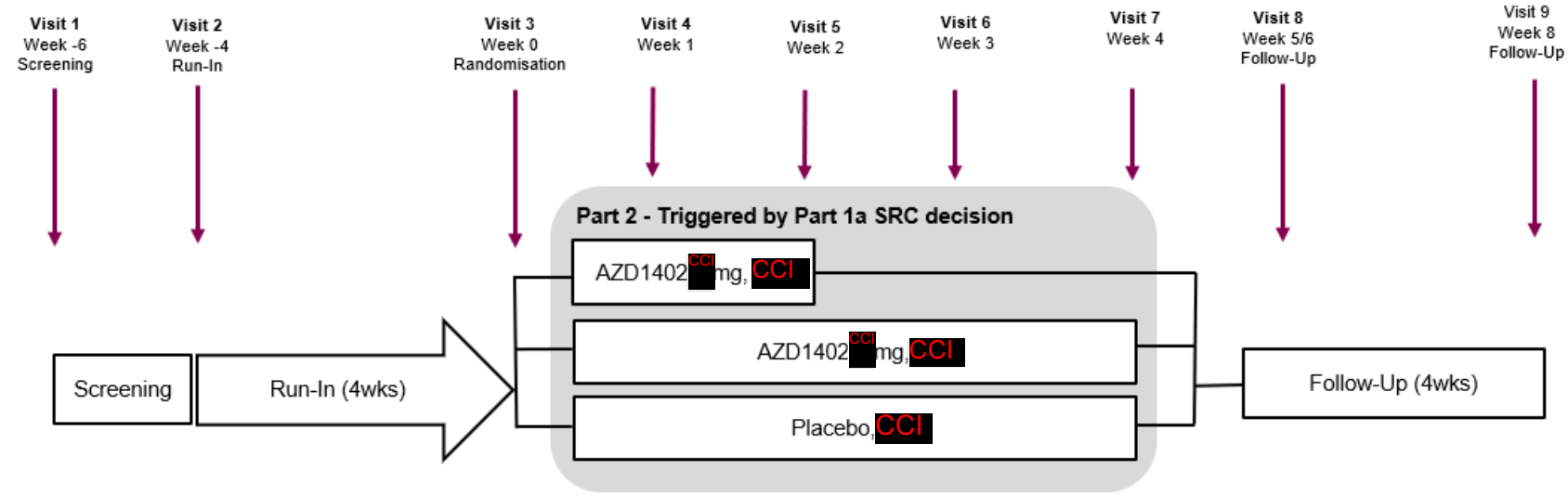
1.2 Schema

Figure 1 Study Design Part 1



CCI SRC = Safety review committee
Participants may also be required to attend a Visit up to approximately 2 years after randomisation for a follow-up ADA sample.

Figure 2 Study Design Part 2



CCI SRC = Safety review committee

1.3 Schedule of Activities

Once informed consent has been obtained, e-Diary provision and training for site and home visits should occur first during Visit 1, followed by PRO assessments. The PRO assessments should be conducted first at all other visits. For all participants, in-clinic spirometry testing must be initiated between 6:00 AM and 11:00 AM during the Screening, Rescreening, and Run-in Period.

Whenever ECGs, vital signs, and blood draws are scheduled for the same nominal time, the order should be as follows: ECGs, vital signs (vital signs can occur immediately after ECG using the same rest period), then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the assigned nominal time.

FeNO and spirometry should follow above assessments. Whenever FeNO and spirometry are scheduled for the same nominal time, the order should be as follows: FeNO followed by spirometry.

Nasal/nasopharyngeal/oropharyngeal sampling should be performed last.

Safety urine samples may be collected at any time during the visit.

If required, the order of assessments may be modified in consultation with the Sponsor Study Physician.

Refer to Section 8 for details on the study assessments.

Table 1 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] – 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Signed informed consent	X														5.1
Admission			X					X							4.1.1
Discharge						X [e]			X						4.1.1
Optional residential stay (throughout Treatment Period)							X								4.1.1
Inclusion and exclusion criteria	X	X	X	X											5.1, 5.2
Demography	X														5.1
Medical/surgical history	X														5.1
Smoking history including cotinine testing	X							X							5.1
Asthma history	X														5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Height/weight [f]	X							X						X	8.2.1
Physical examination	X [g]			X [h]					X [h]			X [g]	X [h]	X [g]	8.2.1
Vital signs (blood pressure, pulse rate, temperature, respiratory rate) [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.2.2
Study drug inhalation training		X	X	X [j]											6.1.3
Home device dispensation (FeNO and spirometer)		X													6.1.2
Home device training (FeNO and spirometer)		X		X [j]											6.1.2

Table 1 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] – 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Rescue medication (eg, salbutamol) [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5.1
FeNO test (in-clinic) [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.3
FeNO at-home assessments (Niox Vero) [l, m]		X				X	X				X	X	X	X	8.1.3
Spirometry (FEV_1 and FVC) [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1
12-lead ECG [o]	X			X	X (Day 7)	X		X							8.2.3
ACQ-6	X	X		X	X (Day 7)	X	X (Day 20)	X				X			8.1.10
FEV_1/PEF (home device) [p]		X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.1, 8.1.11
Cough VAS		X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.10
SPFQ (optional)		X				X						X		X	8.1.10
Assign e-Diary [q]	X														8.1.4
Dispense e-Diary [r]		X													8.1.4

Table 1 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] – 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Check e-Diary compliance			X	X	X	X	X	X	X	X	X	X	X	X	6.4.2
Check compliance with background medication			X	X	X	X	X	X	X	X	X	X	X	X	6.5
Collect e-Diary												X		X	8.1.4
Asthma symptom score and rescue medication use		X	X	X	X	X	X	X	X	X	X	X	X	X	8.1.6, 8.1.7
Study drug dispensation						X									6.1
Study drug administration [s]	CCI														6.1.3
Drug accountability								X				X			6.2
Return unused medication and DPI								X				X			6.2
AEs [t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Blood samples for biochemistry	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for haematology	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for clotting profile	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for CRP (local laboratory) [w]			X	X	X	X	X	X	X	X	X	X	X	X	8.2.4
Blood sample for hs-CRP	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.5.1
Blood samples for safety immuno-biomarkers	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples allergen-specific IgE [x]			X												8.6.1

Table 1 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] – 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Blood samples for serum pregnancy test (all female participants)	X														5.1, 8.2.4
Blood samples for Hepatitis B (HBsAg, anti-HBs, anti-HBc), and C; HIV-1 and HIV-2; QFT for TB [y]	X														5.1, 8.2.4
Blood samples for PK measurements [z]				X	X	X	X	X	X	X	X	X	X	X	8.5.1
Blood samples for ADA [aa]				X		X	X (Day 20, 24)	X				X	X	X	8.5.2
CCI [redacted] [bb]				X											8.6.2, 8.7
CCI [redacted]				X (pre-dose)				X (pre-dose)				X		X	8.6.2
Urinalysis	X	X		X [u]	X [v]	X	X	X		X		X	X	X	8.2.4
Blood samples for FSH (if needed to confirm postmenopausal status in female participants < 50 years and not on HRT)	X														5.1, 8.2.4

Table 1 Schedule of Activities Part 1

Procedure	Screening	Run-in	Treatment Period [a]									ETV/ IPD	Follow-up		Details in CSP Section or Appendix
Visit	**1**	**2**	**3**				**4,5,6**	**7**		**8**	**9**		**10**	**11**	
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**-1**	**1**	**2 to 13**	**14**	**16, 20, 24**	**28 [d] – 2**	**29**	**30**	**32**		**39 ± 6**	**56 ± 4**	
Urine pregnancy test (females of childbearing potential) [cc]			X					X				X		X	5.1, 8.2.4
Urine drug screen	X							X							5.2, 8.2.4
SARS-CoV-2 PCR [dd]	X	X	X [ee]	X	X	X	X	X	X	X	X	X	X	X	5.2, 8.2.4
SARS-CoV-2 serology [dd]	X											X		X	5.2, 8.2.4

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

[a] In-clinic outpatient visits during the Treatment Period will be scheduled so that they fall at the time of morning dose administration.
[b] Time between Visit 1 and Visit 2 may be extended up to 28 days upon input from the Study Physician.
[c] Visit 1 can be done on several/different days prior to Visit 2.
[d] Participants may be admitted on Day 27. Day 28 should be performed on the scheduled calendar day as far as possible; the -2-day window may be utilised only if required. If the -2-day window is utilised, all subsequent visits will be adjusted to follow time window between visits as specified in the SoA.
[e] Discharge on Day 14 after the morning post-dose procedures.
[f] Height only at Visit 1.
[g] A complete physical examination including an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems will be performed.
[h] A brief physical examination including an assessment of the general appearance, skin, abdomen, cardiovascular, and respiratory systems will be performed.
[i] Vital signs to be performed BID whilst participants are in-clinic. Vital signs will be measured pre-dose at the scheduled morning dose in-clinic visits and additionally prior to the evening dose if participants receive the evening dose at the clinic (eg, due to optional overnight stay).
[j] Refresher training as required.
[k] Rescue medication to be as necessary. Check if participant has enough rescue medicine for use at-home use and refill if necessary.
[l] FeNO will be measured pre-spirometry, pre-dose (as applicable), and pre-bronchodilation.

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

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

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

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

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

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

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

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

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

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

[w] CRP must be done locally on Day -1 (may be performed on Day -2 for logistical reasons) to confirm eligibility as per inclusion criterion 26. It may be performed throughout the study in the event of AE/AESI as required to inform suspension/stopping criteria.

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

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

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

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

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

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

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

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

Table 2 Schedule of Activities Part 2

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
Signed informed consent	X											5.1
Inclusion and exclusion criteria	X	X	X									5.1, 5.2
Demography	X											5.1
Medical/surgical history	X											5.1
Smoking history including cotinine testing	X											5.1
Asthma history	X											5.1
Concomitant medication	X	X	X	X	X	X	X	X	X	X		6.5
Height/weight [d]	X						X					8.2.1
Physical examination	X [e]		X [f]				X [f]	X [f]	X [f]			8.2.1
Vital signs (blood pressure, pulse rate, temperature, respiratory rate) [g]	X	X	X	X	X	X	X	X	X	X		8.2.2
Study drug inhalation training		X	X [h]									6.1.3
Home device (spirometer) dispensation		X										6.1.2
Home device training (spirometer)		X	X [h]									6.1.2
Rescue medication (eg, salbutamol) [i]	X	X	X	X	X	X	X	X	X	X		6.5.1
FeNO test (in-clinic) [j]	X	X	X	X	X	X	X	X	X		X	8.1.3
Spirometry (FEV_1 and FVC) [k]	X	X	X	X	X	X	X	X	X		X	8.1.1
Reversibility test [l]	X											8.1.2
12-lead ECG [m]	X		X				X	X				8.2.3
ACQ-6	X	X	X	X	X	X	X	X	X			8.1.10

Table 2 Schedule of Activities Part 2

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
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Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
SPFQ (optional)		X			X			X		X [n]		8.1.10
FEV_1/PEF (home device) [o]		X	X	X	X	X	X		X			8.1.1, 8.1.11
Assign e-Diary [p]	X											8.1.4
Dispense e-Diary [q]		X										8.1.4
Check e-Diary compliance			X	X	X	X	X	X	X	X	X	6.4
Check compliance with background medication			X	X	X	X	X	X	X	X	X	8.1.4
Check compliance with study medication			X	X	X	X	X				X	
Collect e-Diary								X		X		8.1.5
Asthma symptom score and rescue use		X	X	X	X	X	X	X	X			8.1.6, 8.1.7
Study drug dispensation			X		X							6.1
Study drug administration [r]	CCI											6.1
Drug accountability					X		X	X				6.2
Return unused medication and inhaler					X		X	X				6.2
AE [s]	X	X	X	X	X	X	X	X	X	X	X	8.3
Blood samples for biochemistry	X		X [t]		X	X	X	X	X		X	8.2.4
Blood samples for haematology	X	X	X [t]		X	X	X	X	X		X	8.2.4
Blood samples for clotting profile	X											8.2.4
Blood sample for hs-CRP	X	X	X [t]		X	X	X	X	X		X	8.6.1
Blood samples for safety immuno-biomarkers	X		X [t]		X	X	X	X	X		X	8.2.5.1

Table 2 Schedule of Activities Part 2

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
Blood samples allergen-specific IgE [u]			X [u]									8.2.4
Blood samples for CRP (local laboratory) [v]			X	X	X	X	X	X	X	X	X	8.2.4
Blood samples for serum pregnancy test (all female participants)	X											5.1, 8.2.4
Blood samples for Hepatitis B (HBsAg, anti-HBs, anti-HBc), and C; HIV-1 and HIV-2; QFT for TB [w]	X											5.1, 8.2.4
Blood samples for PK measurements [x]			X		X	X	X	X	X		X	8.5.1
Blood samples for ADA [y]			X		X	X	X	X	X	X	X	8.5.1
CCI [z]			X									8.6.2, 8.7
CCI			X [aa]		X [aa]		X [aa]	X	X [aa]			8.6.1
CCI			X [aa]				X [aa]	X	X [aa]			8.6.1
CCI			X [aa]									
Urinalysis	X											8.2.4
Blood samples for FSH (if needed to confirm postmenopausal status in female participants < 50 years and not on HRT)	X											5.1, 8.2.4
Urine pregnancy test (females of childbearing potential) [bb]			X				X	X		X		5.1, 8.2.4
Urine drug screen	X											5.2, 8.2.4
SARS-CoV-2 PCR [cc]	X	X	X	X	X	X	X	X	X	X	X	5.2, 8.2.4

Table 2 Schedule of Activities Part 2

Procedure	Screening	Run-in	Treatment Period [a]					ETV/ IPD	Follow-up		Unscheduled Visit	Details in CSP Section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**		**8**	**9**		
Day	**(up to 14 days before V2) [b,c]**	**-28 ± 2**	**1**	**7 ± 2**	**14 ± 2**	**21 ± 2**	**28 ± 2**		**39 ± 6**	**56 ± 4**		
Week	**-6**	**-4**	**0**	**1**	**2**	**3**	**4**		**5/6**	**8**		
SARS-CoV-2 serology [cc]	X											5.2, 8.2.4

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

[a] In-clinic outpatient visits during the Treatment Period will be scheduled so that they fall at the time of morning dose administration.
[b] Time between Visit 1 and Visit 2 may be extended up to 28 days upon input from the Study Physician.
[c] Visit 1 can be done on several/different days prior to Visit 2.
[d] Height at Visit 1 only.
[e] A complete physical examination including an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems will be performed.
[f] A brief physical examination including an assessment of the general appearance, skin, abdomen, cardiovascular, and respiratory systems will be performed.
[g] Vital signs will be measured pre-dose at the scheduled morning dosing in-clinic visits.
[h] Refresher training if required.
[i] Check if participant has enough rescue medicine for use at-home use and refill if necessary.
[j] FeNO will be measured pre-spirometry, pre-dose (as applicable), and pre-bronchodilation.
[k] Spirometry will be performed 45 minutes and 15 minutes prior to first dose of study intervention on Day 1 and pre-dose at all other visits. If possible, all post-randomisation pre-dose morning clinic device spirometry assessments should be performed within ± 1.5 hours of the time that the 15 min prior to randomisation spirometry was performed.
[l] Reversibility testing will be performed 15 to 30 minutes after inhalation of 400 µg of salbutamol.
[m] ECG will be measured before study drug administration on Day 1 (within 75 min), and 1 hour (± 20 min) after administration of study intervention on post randomisation visits as indicated.
[n] SPFQ (optional) will not be completed at unscheduled visits.
[o] At-home spirometry will be completed up to V8 and only to be completed at non-clinic visit timepoints.
[p] At Visit 1 the e-Diary is set up, participants perform training and ACQ-6 is completed.

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

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

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

[t] Baseline safety sampling will be performed pre-dose on Day 1.

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

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

[w] PCR may be performed to confirm hepatitis B / hepatitis C status if required. Additional evaluation may be required in participants with any signs of active TB at the time of screening or positive interferon-gamma release assay (IGRA, QuantiFERON®-TB Gold) test according to the local standard of care.

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

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

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

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

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

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

2 INTRODUCTION

AZD1402 is being developed as an inhaled therapy for patients with moderate to severe persistent asthma who are not controlled on standard of care therapies. This study will include adults with asthma on medium dose ICS-LABA with the aim to expand the population to include adults with more severe asthma in future studies.

2.1 Study Rationale

The current study aims to assess the efficacy and safety of inhaled AZD1402 administered as a dry powder CCI for 4 weeks in adults with asthma on medium-to-high dose ICS-LABA in a 2-part randomised, double-blind, placebo-controlled, and multi-centre study.

2.2 Background

2.2.1 Asthma

Asthma is a chronic, complex, and heterogeneous respiratory disease characterised by a range of pathogenic features including pulmonary inflammation, mucus hypersecretion, variable airway obstruction, and airway remodelling. It is defined by a history of respiratory symptoms that includes wheezing, shortness of breath, and cough, which vary over time and in severity. Both symptoms and airway obstruction can be triggered by a range of factors including exercise, exposure to inhaled irritants or allergens, or respiratory infections. Symptoms and airway obstruction can resolve in response to therapy or spontaneously, but participants remain at risk of severe worsening of their asthma (exacerbations). These asthma exacerbations can be life-threatening, can significantly impact the participant's quality of life, and result in significant healthcare costs. It has been shown that asthma can be split into distinct clusters or phenotypes based on clinical and pathophysiological characteristics; these include allergic, non-allergic, eosinophilic, obese, late-onset, and severe systemic corticosteroid-dependent phenotypes. The treatment response of participants of different phenotypes varies, highlighting the need to develop new therapies for those participants who are unresponsive to standard of care therapy (Ray, et al. 2016).

2.2.2 Current Therapies

Participants with asthma most often present with symptoms of wheezing, shortness of breath, cough, and chest tightness. The aim of asthma treatment is to achieve good symptom control, and minimise future risk of exacerbations as well as the potential side-effects of treatment International treatment guidelines for asthma recommend ICS as first line therapy (GINA 2022). For individuals who are symptomatic on medium dose ICS monotherapy, step-up therapy with LABAs is the recommended next treatment option followed by other controller therapies including leukotriene receptor antagonists, theophylline, and OCS. 'Biologic agents' (eg, omalizumab and benralizumab) that inhibit specific molecular targets such as IgE or Th2 cytokines and their respective receptors are reserved for those with severe

uncontrolled asthma. For most adults with asthma, a treatment regimen of a controller and bronchodilator therapy provides adequate long-term control. Inhaled corticosteroids are considered the “gold standard” in controlling asthma symptoms and LABAs are the most effective bronchodilators currently available. These agents are often given in combination as research has demonstrated that combination therapy of an ICS with an inhaled LABA provides better asthma control than high doses of ICS alone (Greening, et al, 1994; Woolcock, et al. 1996). Inhaled corticosteroids/LABA combination therapies are the recommended therapy for participants who are not controlled on low doses of ICS alone.

Although the majority of adults with asthma respond to therapy, it is estimated that 5% to 10% of the population with asthma has symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. This severe asthma population accounts for up to 50% of the total asthma health cost through hospital admissions, use of emergency services, and unscheduled physician visits (World Allergy Organisation 2013). Approved treatment options for severe asthma include tiotropium, a long-acting inhaled muscarinic antagonist bronchodilator; omalizumab, an anti-IgE monoclonal antibody; benralizumab, mepolizumab and reslizumab, which are monoclonal antibodies that target the eosinophil chemokine IL-5, and dupilumab, a monoclonal antibody blocker of IL-4Rα which blocks the downstream actions of IL-4 and IL-13. Oral corticosteroids are associated with significant side effects and are therefore not prescribed over longer timeframes. For those adults with moderate/severe asthma who remain uncontrolled on currently approved inhaled or oral treatments, there is a clear unmet need for new therapies before introducing systemic biological treatment. Inhalation, as opposed to systemic and subcutaneous administration of biologics, could offer several potential advantages. In addition to much better convenience for participants, inhaled biologics might require a significantly lower dose, a reduced cost of goods, and hence an expanded participant population. Lower systemic target engagement might also result in better tolerability (Rothe and Skerra, 2018). Inhaled drugs are advantageous as the drug delivery is localised to the lung (target organ) which may allow for a lower dose than needed with systemic delivery. Inhalation is non-invasive, and thus advantageous in terms of ease of use. Current research is focusing on the different pathological mechanisms or endotypes of severe asthma and it is anticipated that this will lead to the development of effective therapies for these subsets of asthma patients.

2.2.3 AZD1402

AZD1402 is derived from human Tlc and is a potent and selective antagonist of IL-4Rα, which antagonises the pro-inflammatory actions of IL-4 and IL-13. AZD1402 is presented as an inhalation powder and belongs to a new class of therapeutics, Anticalin® proteins, which are modified lipocalins. Anticalin proteins are homologous with naturally occurring lipocalins (eg, Tlc and NGAL) and can be generated against a variety of targets using mutation and selection processes. AZD1402 is being developed as an inhaled IL-4Rα antagonist controller

therapy for the treatment of moderate to severe persistent asthma in participants who are not controlled on standard of care therapies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1402 is provided in the IB.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Safety observations from the AZD1402 PK bridging study identified hypersensitivity-like events following a double period of intermittent dosing as part of a cross over study design. During the multiple ascending dose study in untreated participants with mild asthma, several participants experienced respiratory signs and symptoms events such as shortness of breath, dyspnoea; these events could be observed concurrently with FEV_1 decline. These events tended to be associated with higher doses, including the 60 mg nebulised dose not being taken forward. These observations changed the known risk profile of AZD1402. Further characterisation of the safety profile of AZD1402 will be performed in the follow-on studies. The potential risks to participants will be mitigated via safety monitoring activities ongoing throughout the studies, as included in the study design and protocol to ensure the safety of the participants. The benefit or risk to participants is considered to be acceptable.

Detailed information about known and expected potential risks of AZD1402 can be found in the IB.

2.3.1.1 Further Risk Mitigation Approaches

The development of any AE, abnormality in laboratory variables, or any other safety variables will be closely monitored and evaluated on an ongoing basis during this clinical study. Data from all participants will include AEs, clinical chemistry, vital signs, ECG, spirometry (from a safety perspective), and PK.

In the event of respiratory AESIs, FEV_1 decline, or clinically indicated AEs or findings, appropriate tests, including an HRCT scan, could be performed considered to evaluate the potential effect of the study intervention on the airways of participants. Note, ionising radiation carries an increased risk of developing cancer.

This study will include a placebo arm. However, all participants will remain on their current standard of care (or equivalent) and rescue medication as required. Participants will be treated for exacerbations of asthma if they occur and the e-Diary will trigger ‘worsening of asthma alerts’ for participants and research sites.

Participants enrolled in the study will be requested to take protocol-defined asthma medications only, which may include their usual asthma medication or equivalent. All

participants will be provided with a rescue medication (eg, SABA) to be used throughout the Run-in and Treatment Periods, when required. The Investigators will carefully monitor the participants throughout the study, and evidence of worsening of asthma (through study visits and e-Diary recordings of lung function, symptoms, and rescue inhaler use), will trigger an alert to the local clinician as well as the Study Physician. Participants who use daily rescue medication of SABA ≥ 8 puffs for ≥ 3 consecutive days at any time during Run-in Period and before randomisation will be excluded from the study. Participants are free to withdraw from participation in the study at any time. Upon completion of the study, participants' choice of medical therapies are not restricted.

Risk mitigation will be applied as follows: Part 1 will include a safety review step prior to continuation into Part 2. A DSMB will be utilised for the ongoing evaluation of safety during Part 2.

The risks associated of participating this study in the scenario of COVID-19 and the mitigation approaches are detailed in Appendix F.

2.3.2 Benefit Assessment

The purpose of this Phase II, proof-of-concept clinical study is to evaluate the efficacy, safety and tolerability of AZD1402 in adult participants with asthma on medium-to-high dose ICS-LABA. For participants randomised to AZD1402, there is a potential benefit in terms of improvement of their asthma status as indicated by a reduction in the lung inflammation biomarker FeNO seen in Phase I studies. Participants may derive benefit from health assessments (eg, ECG, clinical laboratory safety measurements, and standard of care adherence monitoring) performed as part of the study.

2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimise risk to participants in this study, the potential risks identified in association with AZD1402 are justified by the anticipated benefits that may be afforded to patients with asthma.

Detailed information about the known and expected benefit, potential risks, and mitigation strategies of AZD1402 risks can be found in the IB.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints (Part 1)

Objectives	Outcome Measure
Primary	
• To evaluate the safety and tolerability of AZD1402 compared to placebo at different dose levels in adults with asthma controlled on medium dose ICS-LABA	**Primary safety endpoint:** • Adverse events / AESIs / SAEs with a particular focus on infection, eosinophilia, and hypersensitivity-like events • Vital signs • Changes in clinical chemistry, haematology, and coagulation parameters • Immuno-biomarkers (including but not limited to cytokines, CRP, immunoglobulins including IgE) • ECGs • FEV_1 • FeNO
Secondary	
• To investigate the PK profile and immunogenicity of AZD1402, and associated effects on safety	• PK parameters (full profile in all participants) • ADAs
Exploratory	
• CCI	• Change from baseline in FeNO at Day 28 and average over the Treatment Period • CCI
• To assess the effect of AZD1402 compared to placebo on cough by a VAS in adults with asthma controlled on medium dose ICS-LABA	• Change from baseline average in cough VAS over the Treatment Period
• CCI	• CCI • CCI
• CCI	• CCI • CCI

Table 3 Objectives and Endpoints (Part 1)

Objectives	Outcome Measure
• CCI [redacted]	• CCI [redacted] • CCI [redacted]

Abbreviations: CCI [redacted] ADAs = anti-drug antibodies; AESI = adverse event of special interest; CSR = clinical study report; CRP = C-reactive protein; ECG = electrocardiogram; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; CCI [redacted] ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting beta agonist; CCI [redacted] PK = pharmacokinetics; SAEs = serious adverse events; VAS = Visual Analogue Scale

Table 4 Objectives and Endpoints (Part 2)

Objectives	Outcome Measure
Primary	
• To investigate the efficacy of inhaled AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	**Primary efficacy endpoint:** • Change from baseline in pre-bronchodilator FEV_1 at Week 4
Secondary	
• To further investigate the efficacy of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	• Change from baseline in pre-bronchodilator FEV_1 average over the 4-week Treatment Period • Change from baseline in ACQ-6 at Week 4 and average over the Treatment Period • Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 4 • Change from baseline in average morning PEF over the Treatment Period • Change from baseline in average evening PEF over the Treatment Period • Change from baseline in daily average asthma symptom score (AM/PM) over the Treatment Period
• To investigate the effect of AZD1402 compared to placebo on airway inflammation in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	• Change from baseline in FeNO (in-clinic) at Week 4 and average over the Treatment Period
• To investigate the PK profile and immunogenicity of AZD1402, and associated effects on safety	• PK parameters (sparse in all, full profile in a subset of participants in each treatment arm) • ADAs
• To evaluate the safety and tolerability of AZD1402 compared to placebo in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA	• Adverse events / AESIs / SAEs with a particular focus on infection, eosinophilia, and hypersensitivity-like events • Vital signs

Table 4 Objectives and Endpoints (Part 2)

Objectives	Outcome Measure
	• Changes in clinical chemistry, haematology, and coagulation parameters • Immuno-biomarkers (including but not limited to cytokines, CRP, immunoglobulins including IgE) • ECGs • FEV_1 • FeNO
Exploratory	
• CCI	• CCI • CCI • CCI • CCI • CCI • CCI • Change from baseline in FeNO
• CCI	• CCI CCI
• CCI	• CCI • CCI
• CCI	• CCI CCI

Abbreviations: ACQ-6 = Asthma Control Questionnaire-6; AESIs = adverse events of special interest; ADAs = anti-drug antibodies; AM = before noon (antemeridiem); CRP = C-reactive protein; CSR = clinical study report; ECG = electrocardiogram; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; CCI ICS = inhaled corticosteroids; IgE = immunoglobulin E; LABA = long-acting beta agonist; CCI ; PEF = peak expiratory flow; PK = pharmacokinetics; PM = after noon (post meridiem); SAEs = serious adverse events;

4 STUDY DESIGN

4.1 Overall Design

This is a randomised, placebo-controlled, double-blind, multi-centre, study to assess the efficacy and safety of inhaled AZD1402. The study consists of two parts. Part 1 will be

performed in a Lead-in Cohort to evaluate the safety and PK in a population with asthma controlled on medium dose ICS-LABA before progressing to at-home dosing in adults with asthma who are uncontrolled on medium-to-high dose ICS-LABA in Part 2. Part 2 will be initiated for each dose level following evaluation of safety and PK at the relevant dose level in Part 1a. The study intervention in both parts of the study will be administered CCI using the CCI DPI for a period of 4 weeks.

This study will be conducted in approximately 8-10 countries. The date of first participant screened is estimated to be in December 2020 and the date of last participant last visit is estimated to be in Q3 2023. The entire study period for each participant in both Parts 1 and 2, is approximately 3.5 months; a 2-week Screening Period, a 4-week Run-in Period, 4 weeks of Treatment Period, and 4 weeks of Follow-up Period.

Participants in both parts of the study will receive a handheld e-Diary device which they are required to complete twice daily during the entire duration of the study. Participants will be provided training on the use of the handheld device. Further details on e-Diary is provided in Section 8.1.4.

4.1.1 Part 1

Part 1 of the study will be randomised, double-blind, placebo-controlled, and conducted in parallel for the 2 CCI dose levels (Part 1a) followed by an unblinded safety review and escalation to the CCI dose (Part 1b) dependent on the outcome of the safety review. An unscheduled safety review meeting may also be held in the event of any safety or tolerability events requiring further review that may impact continuation of a cohort or the study (see Appendix A 5.2). Data evaluated in the safety review will be unblinded; however, blinding will be maintained for participants and Investigators. Part 1 will be conducted at approximately 8 study centres.

Part 1a will consist of 30 participants who will be randomised 1:1:1 to receive 1 of the 2 CCI AZD1402 DPI doses (CCI or CCI mg) or placebo in parallel. Part 1b will consist of 15 participants who will be randomised 2:1 to receive the CCI AZD1402 DPI dose (CCI mg) or placebo. Due to logistical reasons, the randomisation in Part 1 will be stratified by site in Australia and Germany.

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

The primary objective in Part 1 is to determine the safety and tolerability of AZD1402 in relation to placebo at 3 different dose levels in adults with asthma controlled on medium dose

ICS-LABA with 4 weeks of dosing and will include assessments of AEs, vital signs, safety blood samples, immuno-biomarkers, ECGs, FEV_1, and FeNO. In addition to clinic spirometry assessments, participants will receive a home spirometry device to use in-clinic and at home as described in the SoAs (Table 1 and Table 2). The secondary objective is to investigate the PK profile and immunogenicity of AZD1402. A full PK and ADA profile will be taken in all participants as per the SoAs (Table 1 and Table 2). Part 1 is not powered for efficacy, but exploratory endpoints will include FeNO and CCI over the 4-week Treatment Period. Additionally cough and CCI The e-Diary will be used to record daily symptoms and questionnaire data.

Participants will sign informed consent prior to participating in any study specific procedures. Visit 1 may be completed over several days prior to Visit 2. If participants are eligible at Visit 1 and the FEV_1 criterion of ≥ 70% predicted and ACQ-6 score of ≤ 1.0 is met, they will return for Visit 2, beginning the Run-in Period. During the Run-in Period, all participants will continue their own stable treatment regime, which will include medium dose ICS-LABA. Treatment must remain stable for the duration of the study, unless clinically indicated adjustments are required.

At Visit 3, Day -1, following the 4-week Run-in Period, participants will be admitted to the clinic. If they remain controlled on a stable dose of ICS-LABA, fulfill the entry criterion of FEV_1 ≥ 70%, and have an ACQ-6 score of ≤ 1.0, the participants will be randomised on the following day as follows:

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

- AZD1402 inhalation CCI mg CCI
- AZD1402 inhalation CCI mg CCI
- Placebo inhalation CCI

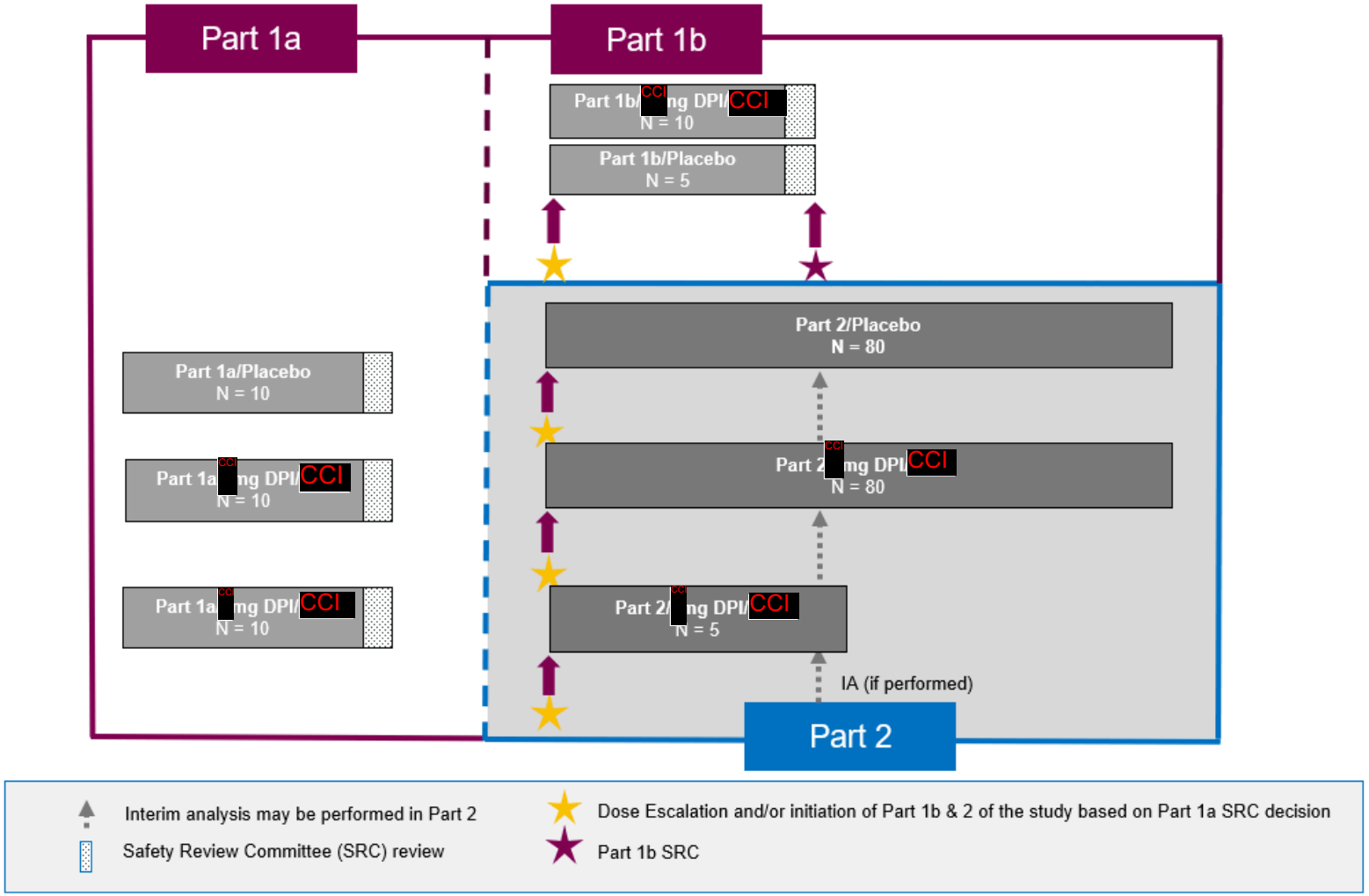
<u>Part 1b Lead-in Cohort</u>

- AZD1402 inhalation CCI mg CCI
- Placebo inhalation CCI

Following randomisation to the 4 weeks of dosing, participants will remain at the clinic for a mandatory residential period of at least 2 weeks followed by 3 outpatient visits (Day 16, 20 and 24). The participants are re-admitted to the clinic on Day 28 and discharged the next day (Day 29) followed by 2 outpatient visits (Day 30 and 32). Additionally, following the minimum 2-week residential period, participants may remain overnight in the clinic any time during Week 3 and Week 4 for any reason. Resuming of dosing following suspension for safety reasons will be performed at the clinic.

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

Figure 3 Dose Staggering and Decision Points Part 1a/b and Part 2



CCI [redacted] DPI = dry powder inhaler; N = number of participants; SRC = Safety review committee

4.1.2 Part 2

Part 2 will be randomised, double-blind, placebo-controlled and will include approximately 165 participants randomised 2:1 (active to placebo) to evaluate 2 inhaled dose levels of AZD1402 versus placebo. Adult participants (age 18 to 75 years, inclusive) with physician-diagnosed uncontrolled asthma treated with medium-to-high dose ICS (total daily dose > 400 µg of budesonide dry powder formulation or equivalent) with LABA (GINA 2022), as maintenance treatment for at least 6 months prior to Visit 1 will be included. ICS-LABA and any additional asthma maintenance controller medications (eg, leukotriene receptor inhibitors, theophylline, LAMA, and chromones) must be stable for at least 4 weeks prior to Visit 1. Standard of care should not include systemic steroid or biologic therapy. Participants will be required to have a FEV_1 of 40% to 85% (inclusive) predicted at Screening, start of Run-in and prior to randomisation (Visits 1, 2 and 3). Participants will also be required to have a blood eosinophil count ≥ 150 cells/µL at Screening, and FeNO ≥ 25 ppb and ACQ-6 score ≥ 1.5 at Screening and randomisation together with documented compliance to ICS-LABA treatment during the 4-week Run-in.

Apart from the scheduled clinic visits, the 4 weeks of dosing in Part 2 of the study will be at home. Part 2 will be started after the unblinded safety review for Part 1a and will be conducted at approximately 68 study centres.

The primary objective in Part 2 of the study is to determine the efficacy of AZD1402 after 4 weeks of dosing as assessed by change from baseline in pre-bronchodilator FEV_1 compared to placebo. The study will recruit participants receiving treatment with medium-to-high dose ICS-LABA at Screening and in order to ensure a balanced distribution across the treatment arms; the randomisation of participants will be stratified by country.

Participants will sign informed consent prior to participating in any study specific procedures. Visit 1 may be completed over several days prior to Visit 2. If participants are eligible at Visit 1 with a confirmed asthma diagnosis and FEV_1 criteria (≥ 40% to ≤ 85% predicted) are met, they will return for Visit 2, beginning the Run-in Period. During the Run-in Period, all participants will continue their standard of care including ICS-LABA. The ICS-LABA dose must remain stable for the duration of the study, unless clinically indicated adjustments are required.

At Visit 3, following the 4-week ICS-LABA Run-in, participants who remain uncontrolled, as assessed by an ACQ-6 score of ≥ 1.5 (Visit 1 and Visit 3), pre-bronchodilator FEV_1 of 40% to 85% (inclusive) at baseline (Visit 3), and FeNO ≥ 25 ppb (Visit 1 and Visit 3) will be randomised to 1 of 3 possible treatment arms. Eighty participants will be randomised to the [redacted] mg dose and placebo, respectively. Approximately 5 participants will be randomised to [redacted] mg dose arm:

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

The primary assessment of efficacy is measured by the change in pre-bronchodilator FEV_1 from baseline (Visit 3), as compared to placebo in the 4-week Treatment Period (Visit 7). Secondary assessments of efficacy include FeNO, PEF, ACQ-6 and daily symptoms as recorded in the e-Diary. [redacted]

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

Pharmacokinetic sampling (sparse sampling in all, full profile in a subset of approximately 25% of participants per treatment arm) will be performed. In Part 2 an interim analysis may be performed which will be evaluated by the URC.

For both Parts 1 and 2, in addition to the PK, blood samples for ADA assessment will be collected in all participants. Blood samples and nasal/nasopharyngeal/oropharyngeal swabs may be collected for diagnosis of COVID-19 and identification of SARS-CoV2 antibodies as indicated in the SoAs. Clinical monitoring of any suspected hypersensitivity events may prompt unscheduled assessments of safety parameters, including FEV_1, FeNO, CRP, routine safety blood samples, ADA, immuno-biomarkers, and PK. [redacted]

Spirometry, FeNO measurement, ECG, and ACQ-6 will be performed at site visits as indicated in the SoAs (Table 1 and Table 2). Spirometry measurements will also be performed in-house and at home as well as daily e-Diary entries and rescue medication use. Home FeNO measurement and cough VAS will be performed in Part 1.

Safety variables (including AEs, safety laboratory parameters, and lung function) will be continually evaluated.

If required for safety reasons/COVID-19 mitigation, home sampling and assessments may be conducted for any of the scheduled visits (Appendix F).

In order to provide an independent periodic review of safety throughout the study, in addition to the ongoing, blinded review provided by the Sponsor/Designee Medical Monitor for detection of any potential safety signals, an unblinded DSMB will be utilised for Part 2 of the study. Set up of the DSMB, and frequency of data transfer will be described in the DSMB Charter. The DSMB will make any necessary recommendations regarding further conduct of the study based on their evaluation of emerging data in Part 2 of the study. Additionally, an unblinded SRC, including the Sponsor study team will review PK and unblinded safety data following completion of Part 1a before progressing to Part 1b/2, and following completion of Part 1b.

Refer to Appendix A 5 for details on different committees involved in this study.

4.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARSCoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent or reconsent for the mitigation procedures (note, in the case of verbal consent or reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed once in previously screened participants

once if there is reason to believe the reason for screen failure was temporary. It is only permitted to rescreen more than once for logistical reasons.

- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IMP administration.
- At-home study procedure: Performed by a qualified HCP from the study site or TPV service.
- Additional information that cannot be obtained via a site visit can be obtained via telemedicine.
- Centralised assessments may be performed locally.

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

4.1.4 Study Conduct Mitigation During SARS-CoV-2 Pandemic

In case of local or global SARS-CoV-2 outbreaks, appropriate risk assessments and mitigation measures will need to be taken into consideration to protect participants and health care professionals involved in the clinical trial and ensure data quality as per regulatory agencies and local guidelines.

If, for reasons related to the COVID-19 pandemic (eg, local lockdown, self-isolation requirements), a participant is not able to attend their scheduled visit within the visit window, they can have their visit rescheduled as per agreement with the Sponsor Study Physician. Additionally, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow collection of data for AEs and ensure continuous medical care and oversight. The term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices. Applicable measures for source data verification, if on-site monitoring at the trial sites is not indicated due to the coronavirus pandemic should be implemented.

For further details on study conduct during SARS-CoV-2 or similar pandemic refer to Appendix F.

4.2 Scientific Rationale for Study Design

A placebo-controlled, double-blind design has been chosen to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study arising from the influence that the knowledge of treatment may have on the recruitment and

allocation of participants. The inclusion of a placebo arm is considered the most reliable method to minimise participant and Investigator bias and is also recommended by the EMA regulatory guidance in the design of dose-finding studies for moderate-severe asthma.

The efficacy endpoints chosen in this study are commonly measured endpoints in asthma studies. Spirometry is one of the fundamental outcome measures used in asthma studies. It provides an objective and highly reproducible measure of airflow limitation caused by smooth muscle contraction or structural changes. Forced expiratory volume in 1 s is recommended as the primary endpoint for studies of bronchodilator therapy by the ATS and the ERS in their official statement on asthma control and exacerbations (Reddel, et al. 2009). The ACQ is also widely regarded as a useful measure that includes some core asthma symptoms and symptom-related clinical markers of asthma. Traditionally, PEF, occurrence of exacerbations, use of rescue medication, markers of airway inflammation as assessed by FeNO, and participant reported symptoms scores are also among the different measures used to assess the efficacy of asthma interventions in clinical trials (GINA 2022). CCI [redacted]

4.3 Justification for Dose

The proposed inhaled doses of AZD1402 in this study are CCI [redacted] mg CCI [redacted]

The doses in the relevant range were selected considering the following data from previous clinical studies:

- CCI [redacted]
- CCI [redacted]

CCI [redacted]

Safety and tolerability data from previous studies with AZD1402 support ongoing development with step-wise dose increase as described in the current study design.

4.4 End of Study Definition

For the purpose of CTT the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the SoAs (Table 1 and Table 2).

4.4.1 Premature Termination of the Study and Stopping Criteria

The Sponsor will suspend or terminate a dose level or the entire study (as applicable) following the review of all available safety data if any of the following occurs at the dose or study level:

Per dose level (Part 1)

- Two participants experience a FEV_1 drop ≥ 30% from baseline (in-clinic)* attributable to AZD1402.
- One participant experiences a hypersensitivity-like SAE attributable to AZD1402.

- Day 28 exposure in one participant in Part 1 exceeds or is predicted to exceed (for Part 1b) a peak concentration Cmax of 5420 ng/mL or exposure AUC(0-24 h) of 68700 ng.h/mL.

*Baseline Part 1: Mean of Day -1 and Day 1.

Per dose level (Part 2)

- Clinically significant FEV_1 decline from baseline* attributable to AZD1402 comparing the number of participants reaching a FEV_1 drop $\geq$ 30% in active versus placebo as assessed by the DSMB.
- One participant experiences a hypersensitivity-like SAE attributable to AZD1402.

*Baseline Part 2: Mean of Day 1 (15 minutes and 45 minutes pre-dose).

Study level

- Two participants experience a hypersensitivity-like SAE and/or severe hypersensitivity event attributable to AZD1402.
- The overall safety and tolerability profile as determined by the DSMB does not justify continuation with dosing as per the current protocol.
- Significant immunogenicity impacting safety and tolerability.
- The Sponsor considers the applied doses of the study intervention to be no longer relevant.
- The Sponsor decides to discontinue the study.
- Data not known before, become available and raise concern about the safety of AZD1402 so that continuation would pose potential risks to the participants.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Note: Visit 1 and Visit 2 assessments (Table 1 and Table 2) can be repeated once (within 1 week of the original visit for Visit 2), but only if the Investigator believes that a repeat visit may allow the participant to become eligible to enter the study and the screening window is maintained. CRP may be repeated for the duration of the run-in period to inform V2 eligibility for randomisation. Run-in may be extended on a case-by-case basis at the discretion of the Sponsor in the event of logistical challenges.

5.1 Inclusion Criteria

Participants will be enrolled into this study only if they meet all of the following inclusion criteria:

Age

1 Participants 18 to 75 years (inclusive) of age, at the time of signing the informed consent at Visit 1.

Type of Participant and Disease Characteristics

2 Participants who have a documented clinical diagnosis of asthma for ≥ 12 months before Visit 1.

3 Participants who are able to perform acceptable pulmonary function testing for FEV_1 according to ATS/ERS acceptability criteria.

4 Participants who are able to demonstrate the ability to use the study inhalation device properly (at Visit 2).

Weight

5 Body mass index within the range 18 to 35 kg/m^2 (both inclusive).

Sex

6 Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

(a) Male participants must be surgically sterile or agree to use highly-effective contraceptives for the entire duration of the study (from the time they sign the informed consent), or for 3 weeks after the last dose of study intervention, whichever is longer. Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone where spermicides are not approved) from the time they sign the informed consent for the duration of the study or for 3 weeks after the last dose of the study intervention, whichever is longer. It is strongly recommended for the female partner of a male participant to also use a highly-effective method of contraception (described below) throughout this period.

(b) Female participants:

- All female participants must have a negative serum pregnancy test at Screening. Female participants are considered to be of non-childbearing potential, if they are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or postmenopausal. Women will be considered postmenopausal

if they have been amenorrhoeic for ≥ 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:

  - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
  - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment. Women who are considered to be postmenopausal without documentation of 12-month amenorrhea and receiving HRT, will have to use one of the non-hormonal highly-effective contraception methods in addition to HRT, or discontinue HRT and to use hormonal highly-effective method for at least 3 months prior to Visit 1, Screening Period.

- Female participants of childbearing potential
  - must have a negative urine pregnancy test before the administration of first dose of study intervention and
  - must agree to use a highly-effective method of birth control (confirmed by the Investigator) from randomisation throughout the study duration or for 3 weeks after the last dose of study intervention, whichever is longer.

NOTE: Highly-effective methods of birth control (those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

- Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Sexual abstinence, ie, refraining from heterosexual intercourse (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant).
- Vasectomised sexual partner provided that partner is the sole sexual partner of the study participant and that the vasectomised partner has received medical assessment of the surgical success.

Informed Consent

7 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

8 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

Others

9 Participant is a non-smoker or an ex-smoker (this includes marijuana, e-cigarettes or inhaled tobacco products and must have quit ≥ 3 months before Visit 1) with a total smoking history of less than 10 pack-years (not applicable for e-cigarettes).

10 Participant is willing and able to follow study procedures and restrictions.

In addition to the above, participants should meet all the specific inclusion and randomisation criteria for respective parts of the study as listed below.

5.1.1 Part 1-specific Inclusion Criteria

11 Documented treatment with medium dose ICS with LABA for at least 6 months prior to Screening (Visit 1) (ICS equivalent of budesonide dry powder formulation > 400 to 800 µg/day).

12 ICS and LABA must be on a stable dose for at least 3 months prior to Visit 1, during Screening and Run-in Periods and may be contained in a combination product or separate inhalers.

13 No asthma exacerbations in last 12 months requiring oral or IV steroids or hospitalisation/ emergency room visit due to asthma.

14 Pre-bronchodilator FEV_1 ≥ 70% predicted at Screening (Visit 1) and start of Run-in (Visit 2). Prior to spirometry, the following medication withhold periods should be observed:

(a) SABA for at least 6 hours.

(b) Twice daily LABA-containing therapies for at least 12 hours.

(c) Once daily LABA-containing therapies for at least 24 hours.

15 Asthma Control Questionnaire 6 score of ≤ 1.0 at Screening (Visit 1) and start of Run-in (Visit 2).

5.1.2 Part 2-specific Inclusion Criteria

16 Documented evidence of asthma as demonstrated by any of the following:

(a) Post-BD reversibility of $FEV_1 \geq 12\%$ and ≥ 200 mL within 5 years prior to Visit 1, or at Visit 1, or

(b) PEF average daily variability > 10% over a 2-week period within 5 years prior to Visit 1, or

(c) Variability of $FEV_1 \geq 12\%$ and ≥ 200 mL between any two clinical visits within 5 years prior to Visit 1, or

(d) Positive bronchial challenge test within 5 years prior to Visit 1. A positive test is defined as a fall in FEV_1 from pre-challenge of $\geq 20\%$ with standard doses of methacholine or histamine, or $\geq 15\%$ with standardized hyperventilation, hypertonic saline or mannitol challenge, or

(e) Positive exercise test within 5 years prior to Visit 1. A positive test is defined as a fall in FEV_1 of > 10% and > 200 mL from pre-challenge.

17 Documented treatment with medium-to-high dose ICS-LABA for at least 6 months prior to Screening (Visit 1) (ICS equivalent of budesonide dry powder formulation > 400 μg/day). ICS and LABA must be on a stable dose for at least 4 weeks prior to Visit 1, during Screening and Run-in Periods.

18 If on asthma maintenance controller medications in addition to ICS-LABA, the dose of the additional controller medications (eg, leukotriene receptor inhibitors, theophylline, LAMA, and chromones) must be stable for at least 4 weeks prior to Visit 1, during Screening and Run-in Periods.

19 Pre-bronchodilator FEV_1 of 40% to 85% (inclusive) predicted at Screening (Visit 1) and start of Run-in (Visit 2).

20 Blood eosinophil count of ≥ 150 cells/μL and FeNO ≥ 25 ppb at Screening (Visit 1).

21 Asthma Control Questionnaire 6 score ≥ 1.5 at Screening (Visit 1).

5.1.3 Part 1-specific Randomisation Criteria at Visit 3

22 Pre-bronchodilator $FEV_1 \geq 70\%$ predicted.

Prior to spirometry, the following medication withhold periods should be observed:

(a) SABA for at least 6 hours.

(b) Twice daily LABA-containing therapies for at least 12 hours.

(c) Once daily LABA-containing therapies for at least 24 hours.

23 At least 70% compliance with usual asthma controller ICS-LABA during Run-in Period (from Visit 2 to Visit 3) based on daily e-Diary.

24 Minimum 80% compliance with ePRO completion. 80% compliance is defined as completing daily e-Diary for any 8 mornings and any 8 evenings of the last 10 days of the Run-in Period.

25 Asthma Control Questionnaire 6 score of ≤ 1.0.

26 C-reactive protein < 5 mg/L on Day -1.

5.1.4 Part 2-specific Randomisation Criteria at Visit 3

27 Pre-bronchodilator FEV_1 of 40% to 85% (inclusive) predicted.

Prior to spirometry, the following medication withhold periods should be observed:

(a) SABA and SAMA for at least 6 hours.

(b) Twice daily LABA and/or LAMA-containing therapies for at least 12 hours.

(c) Once daily LABA and/or LAMA-containing therapies for at least 24 hours.

(d) LTRA for at least 24 hours.

(e) Twice daily theophyllines for at least 12 hours.

(f) Once daily theophyllines for at least 24 hours.

28 Asthma Control Questionnaire 6 score of ≥ 1.5.

29 At least 70% compliance with usual asthma controller ICS-LABA during Run-in Period from (Visit 2 to Visit 3) based on daily e-Diary.

30 Minimum 70% compliance with ePRO completion. 70% compliance is defined as completing daily e-Diary for any 7 mornings and any 7 evenings of the last 10 days of the Run-in Period.

31 C-reactive protein < 10 mg/L at Visit 2.

32 A FeNO of ≥ 25 ppb.

5.2 Exclusion Criteria

Participants are excluded from inclusion in the study if any of the following criteria apply:

Medical Conditions

1 Women who are pregnant or breastfeeding, or who are planning to become pregnant during the study.

2 Known or suspected hypersensitivity including anaphylaxis/anaphylactoid reaction following any biologic therapy, or known history of drug hypersensitivity to any component of the study intervention formulation.

3 Evidence of any active clinically important pulmonary disease, other than asthma, within 5 years at screening (eg, active lung infection, COPD, bronchiectasis, idiopathic pulmonary fibrosis, cystic fibrosis, lung cancer, alpha-1 antitrypsin deficiency, etc.).

4 History of pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis).

5 History or clinical suspicion of any clinically relevant or active disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or influence the results or the participant's ability to participate in the study, or any other safety concerns in the opinion of the Investigator.

6 History of severe COVID-19 infection requiring hospitalisation within the last 12 months or clinical history compatible with long COVID (symptoms beyond 12 weeks of acute infection).

7 Confirmed symptomatic COVID-19 infection during Screening, Run-in or prior to randomisation. Participants can be rescreened once recovered if infection is not severe. Participants who are asymptomatic with a positive COVID-19 test could continue in Screening if a repeat test done according to applicable local guidelines is negative within the screening window.

8 Current malignancy or history of malignancy, except for:

(a) Patients who have had basal cell carcinoma, localized squamous cell carcinoma of the skin or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date of informed consent, and assent when applicable, was obtained.

(b) Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date of informed consent.

9 Significant history of recurrent or ongoing 'dry eye', which has been diagnosed and treated with medications prescribed by an Ophthalmologist.

10 Diagnosis of Sjögren's syndrome.

11 High risk of infection suggesting abnormal immune function, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per Investigator's judgment.

12 History of, or known significant infection or positivity at Visit 1, Screening Period, including hepatitis B or C, or HIV, that may put the participant at risk during participation in the study. Participants with positive anti-HBsAg test, a negative HBsAg test and a negative hepatitis B core total test at Screening may be included into the study if they have a positive hepatitis B vaccination history. Participants where the interpretation of the hepatitis B panel results is inconclusive, may be included following the confirmation of a negative PCR test. Participants who test positive for anti-hepatitis C antibody may be enrolled if their hepatitis C virus RNA test result is negative in the absence of cirrhosis.

13 Evidence of active TB in the opinion of the Investigator. Participants with a recent first-time (within 2 years) or newly positive interferon gamma release assay (IGRA, QuantiFERON®-TB Gold) test need to complete an appropriate course of treatment as considered by the Investigator per local guidelines/standard of care before being

considered for inclusion. Evaluation may consist of history, physical examinations, imaging and/or TB tests as determined by local guidelines.

14 Clinically significant lower respiratory tract infection not resolved within 4 weeks prior to Screening and during Run-in, as determined by the Investigator.

15 Clinically significant upper respiratory tract infection at Screening and during Run-in, as determined by the Investigator.

16 A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent is obtained, that has not been treated with, or has failed to respond to standard of care therapy.

17 Any clinically important ECG abnormalities obtained during the Screening/Run-in Period, which in the opinion of the Investigator may put the participant at risk or interfere with study assessments.

18 Any clinically significant cardiac disease:

(a) Acute coronary syndrome (acute myocardial infarction, unstable angina), coronary intervention with percutaneous coronary intervention / coronary artery bypass surgery or stroke within 6 months.

(b) Heart failure NYHA II-IV.

(c) Untreated high degree atrioventricular-block (≥ 3:1 conduction rate / Grade III block) / significant sinus node dysfunction / pause or therapy requiring tachyarrhythmia.

(d) Family history of long QT-syndrome.

(e) Hypertrophic cardiomyopathy or clinically significant valvular heart disease.

19 Uncontrolled hypertension with BP > 150/90 mmHg.

20 History of life-threatening asthma attack or asthma attack requiring ventilation.

21 **Part 2 only:** History of 3 or more severe asthma exacerbations (defined as a worsening of asthma requiring treatment with systemic corticosteroids for 3 days or more, or hospitalisation/emergency room visit due to asthma) in the 12 months prior to Visit 1.

22 Daily rescue use of SABA ≥ 8 puffs for ≥ 3 consecutive days at any time during Run-in Period, before randomisation.

23 History of anaphylaxis that required the use of epinephrine or hospitalisation.

24 Any clinically significant abnormalities in haematology.

25 Alanine aminotransferase or AST level ≥ 3 times the ULN, confirmed by repeated testing during Screening Period. Transient increase of AST/ALT level that resolves by the time of randomisation is acceptable if in the Investigator's opinion, the participant does not have an active liver disease and meets other eligibility criteria.

26 History of, or reason to believe a participant has a history of, drug or alcohol abuse within the past 2 years prior to Screening as judged by the Investigator which may include a

positive drugs of abuse test not consistent with the participant's acute or chronic treatment.

27 Planned in-patient surgery, major dental procedure or hospitalisation during the study.

Prior/Concomitant Therapy

28 Systemic corticosteroid use within the 6 weeks before Visit 1, Screening Period and during Run-in.

29 Participants who have previously received AZD1402.

30 Treatment with marketed or investigational biologicals such as monoclonal antibodies or chimeric biomolecules, and within 6 months or 5 half-lives before Visit 1, Screening Period and during Run-in, which includes but is not limited to:

(a) Anti-IgE (eg, omalizumab).

(b) Anti-IL5 and anti-IL5R (eg, mepolizumab, reslizumab, benralizumab).

(c) Anti-IL4R (eg, dupilumab).

31 Any investigational nonbiologic drug within 60 days (or 5 half-lives, whichever is longer) prior to Visit 1 and during Run-in.

32 Any immunosuppressive therapy (other than systemic corticosteroids) within 3 months of Visit 1, Screening Period and during Run-in.

33 Live or attenuated vaccine within 4 weeks of Visit 1, Screening Period and during Run-in.

34 Receipt of COVID-19 vaccine (vaccine or booster dose) within 30 days prior to randomisation.

35 Immunoglobulin or blood products within 4 weeks of Visit 1, Screening Period and during Run-in.

36 Any immunotherapy within 3 months of Visit 1, Screening Period and during Run-in, except for stable maintenance dose allergen-specific immunotherapy started, at least 4 weeks prior to Visit 1 and expected to continue through to the end of the Follow-up Period.

37 **Part 1 only:** Additional asthma maintenance controller medications in addition to ICS-LABA (eg, leukotriene receptor inhibitors, theophylline, LAMA, chromones) within 3 months of Visit 1, Screening Period and during Run-in.

Other Exclusions

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

39 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

40 Donation of blood (≥ 450 mL) within 3 months or donation of plasma within 14 days before Visit 1, Screening Period.

41 Previous participation or prior screen failure in the current study unless for reasons specified in the protocol, or participation in any other research study within 1 month prior to Visit 1.

42 Vulnerable persons (eg, persons kept in detention).

5.3 Lifestyle Considerations/Restrictions

5.3.1 Meals

1 Participants should avoid eating a large meal for at least 2 hours prior to all spirometry and FeNO assessments at the site.

2 Participants should not eat or drink 1 hour prior to having FeNO assessment.

5.3.2 Caffeine and Alcohol

1 For Part 1, participants should abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 4 hours prior to Screening, baseline, and morning in-clinic spirometry assessment. For Part 2, participants should abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) during the Treatment Period, for 4 hours prior to in-clinic spirometry assessment.

2 During the residential Treatment Period, participants should abstain from alcohol for 24 hours before admission until discharge.

5.3.3 Activity

1 Participants should avoid engaging in strenuous exercise at least 2 hours prior to all spirometry and FeNO assessments, both in-clinic and at home.

5.3.4 Others

1 Participants should abstain from donating blood and plasma from the time of informed consent until the final Follow-up Visit or 28 days of study intervention in the case of early termination.

2 It is recommended that participants' pneumonia / influenza vaccinations are up to date as per local guidelines.

3 Maintenance and Reliever Therapy (MART) regime is not permitted for the duration of the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if there is reason to believe the reason for screen failure was temporary. The timing of the Rescreening should be determined by the Investigator, taking into account the initial reason for screen failure. Rescreened participants should be assigned the same participant number as for the initial Screening. It is only permitted to rescreen more than once for logistical reasons. In the case of more than one rescreening, a different participant number should be assigned.

Prior to Rescreening, participants must be reconsented.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 5 Investigational Products

Intervention name	**AZD1402**	**Placebo**	**SABA (rescue medication)**	**Run-in medications (ICS-LABA combination) (if applicable)**
Type	Drug	Drug	Drug	Drug
Dose formulation	Inhalation powder CCI	Inhalation powder CCI	Inhalation aerosol by MDI	Inhalation powder
Unit dose strength(s)	CCI mg, CCI mg, and CCI mg	NA	100 µg	Depends on particular medication
Dosage level(s)	CCI mg, CCI mg, and CCI mg, all CCI	NA	100 µg per nominal dose 90 µg per nominal dose PRN	As required
Route of administration	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation
Use	experimental	placebo	rescue medication	standard of care
IMP and NIMP	IMP	IMP	NIMP	NIMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided locally by the study site	Provided locally by the study site
Packaging and labelling	Provided in labelled patient kits (1 capsule in labelled CCI placed in labelled container/box). Patient kits will be labelled in accordance with GMP Annex 13 and per country regulatory requirement	Provided in labelled patient kits (1 capsule in labelled CCI placed in labelled container/box). Patient kits will be labelled in accordance with GMP Annex 13 and per country regulatory requirement	Provided in labelled kits in accordance with GMP Annex 13 and per country regulatory requirement	Provided in labelled kits in accordance with GMP Annex 13 and per country regulatory requirement

Abbreviations: CCI GMP = Good Manufacturing practice; CCI ICS = inhaled corticosteroids; IMP = Investigational Medicinal product; LABA = long-acting beta agonists; MDI = multiple dose inhaler; NA = Not applicable; NIMP = non-investigational medicinal product; PRN = pro re nata (as required); SABA = short-acting beta antagonist

6.1.2 Medical Devices

1 Medical devices (not manufactured by or for Sponsor) provided for use in this study are.
   - CCI DPI (Status, Approved/CE Marketed).
   - CCI (Status, Approved/CE Marketed).
   - Spirometer FEV_1/PEF measuring device (Status, Approved/CE Marketed).

2 Instructions for medical device use are provided in the Investigator Manual.

3 All medical device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the Investigator throughout the clinical investigation (see Section 8.3.12) and appropriately managed by the Sponsor.

6.1.3 Dose and Treatment Regimens

In Part 1 and in Part 2 at Visit 2 and Visit 3 (refresher training if appropriate), participants will receive training to use the DPI for AZD1402 or placebo using appropriate DPIs not containing AZD1402, for that purpose. Retraining on the DPIs as well as other medical devices will be provided to the participants on any of their visits to the clinic as and when required. Participants will be asked to record their intake of study intervention daily in their e-Diary.

6.1.3.1 Throughout the Study

In addition to study intervention, all participants will be provided with a SABA as rescue medication (eg, salbutamol/albuterol), to be used throughout the Run-in and Treatment Periods. All participants should refrain from taking a SABA as rescue medication 6 hours prior to pulmonary function tests.

6.1.3.2 Run-in Period

The Run-in Period will be 4 weeks long. During this period, the participants are required to maintain their ICS-LABA dose.

6.1.3.3 Treatment Period

The Treatment Period will be 4 weeks long with the study intervention administered CCI Controller medications (eg, ICS-LABA) should remain at a stable dose and be taken after the CCI study intervention as applicable.

In Part 1 on Days 1 to 14 and Day 28, controller medication will be taken 2 hours after study intervention CCI If patients are not discharged on Day 14, but remain in the unit during Days 15 to 27, controller medication will continue to be taken 2 hours after study intervention CCI At all other timepoints in Part 1, controller medication will be taken directly after study intervention, including CCI doses and on re-admission to the unit on Days 15 to 27

post discharge (ie, controller medication timing will remain unchanged from home dosing). The timing of the controller medication in Part 1 may be adjusted by the Sponsor.

6.2 Preparation/Handling/Storage/Accountability

1 The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

3 The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Investigator's Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants will be centrally assigned to randomised study intervention using an IRT/RTSM.

The IRT/RTSM will provide to the Investigators or pharmacists the kit identification number to be allocated to the participants at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual that will be provided to each site.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's study intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analysis of data until all decisions on evaluability of the data from each individual participant have been made and documented.

The laboratory vendor personnel performing the bioanalyses of the serum samples will have access to the randomisation list.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention under medical supervision and witnessing the study intervention administration. The date and time, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.4.1 Study Intervention Compliance

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by checking the daily e-Diary and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF. Compliance is expected to be ≥ 80% during the Treatment Period. Retraining is to be performed for those participants who demonstrate lower compliance.

6.4.2 E-Diary Compliance

The expected compliance with the e-Diary in both Run-in and Treatment Periods is at least 80% of days in Part 1 and at least 70% of days in Part 2. Participants with < 80% e-Diary compliance during Run-in Period in Part 1 as well as participants with < 70% e-Diary compliance during Run-in Period in Part 2 will not be randomised.

Reminding or retraining of the participant on proper e-Diary documentation will be conducted if there is a discrepancy between the drug accountability data and e-Diary entries.

A record of the number of medication and inhalers dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Medication start and stop dates, including dates for medication delays and/or dose reductions will also be recorded in the eCRF. In the event that e-diary cannot be completed due to technical problems, the run-in may be prolonged, at Sponsor’s discretion.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins,

and/or herbal supplements [or other specific categories of interest)] that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

The study will recruit participants receiving treatment with medium dose ICS with LABA for Part 1 and participants receiving treatment with medium-to-high dose ICS with LABA for Part 2 (separate inhalers or combination product). During Run-in, all participants in Part 1 will continue on their own medication of medium dose ICS with LABA. This standard of care medication must remain stable for the duration of the study, including a 4-week Treatment Period and a 4-week Follow-up Period, unless clinically indicated adjustments are required.

Participants must be instructed to inform the Investigator of plans to take any new treatment during the participation in the study, including over-the-counter medicinal and herbal products.

6.5.1 Rescue Medication

The study site will provide the participants with rescue medication (SABA; salbutamol, 100 µg per nominal dose and albuterol, 90 µg per nominal dose, US) starting from the Screening Visit.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.5.2 Required Medication

Participants should continue to use the following controller medications at stable dose and regimen throughout the study as per their individual requirements, with the exception of medication withhold periods described in Section 6.5.3.

- Medium dose ICS (Part 1), medium-to-high dose ICS (Part 2).
- LABA.
- Part 2 only: any additional asthma controller therapies in use at time of Screening, eg, LAMA, LTRA, theophylline, Chromones. Standard of care should not include systemic steroid or biologic therapy.

6.5.3 Medication Withhold Periods

In Part 1 and following randomisation, participants should withhold the following medications for the specified times prior to scheduled spirometry and FeNO measurements at site:

- SABAs and SAMAs for at least 6 hours, where possible.
- Twice daily LABA-containing therapies should be taken after study intervention with the aim to have a withhold period of approximately 10 to 12 hours.
- Once daily LABA-containing therapies should be taken after study intervention with the aim to have approximately 22 to 24 hours prior to the morning assessment.

Additionally, participants should withhold SABA for 6 hours prior to at-home spirometry assessments, where possible. Controller medication should be taken after study intervention as applicable CCI [redacted] Details of timing of controller medication are provided in Section 6.1.3.3.

Note: Screening, start of Run-in, baseline, and Day 28 withhold period for pre-bronchodilator FEV_1 should be at least 6, 12 or 24 hours for SABA, twice daily LABA, or once daily LABA respectively.

In Part 2, participants should withhold the following medications for the specified times prior to scheduled spirometry and FeNO measurements at the clinic scheduled visits.

- SABAs and SAMA for at least 6 hours.
- Twice daily LABA and/or LAMA-containing therapies for at least 12 hours.
- Once daily LABA and/or LAMA-containing therapies for at least 24 hours.
- LTRA for at least 24 hours.
- Twice daily theophylline for at least 12 hours.
- Once daily theophylline for at least 24 hours.

Additionally, participants should withhold SABA for 6 hours and all bronchodilator medications for 8 hours prior to at-home spirometry assessments, where possible. Controller medication should be taken directly after study intervention as applicable CCI [redacted]

6.5.4 Restricted and Prohibited Medications

The following medications are restricted from Visit 1 (Screening) to the end of the Follow-up Period, unless clinically indicated, as determined by a physician:

- Acute systemic (oral or injectable) corticosteroids within 6 weeks of Visit 1 until the end of the Follow-up Period, except for treatment of acute exacerbations of asthma during the course of the study.

The following medications are prohibited in Part 1:

- Leukotriene receptor inhibitors
- Inhaled short- and long-acting anticholinergics
- Combination of SABA and SAMA
- Xanthines
- Inhaled chromones
- Oral and inhaled beta2 agonists (except salbutamol/albuterol used as rescue medication)

The following medications are prohibited in Part 1 and Part 2:

- Marketed or investigational biologicals such as monoclonal antibodies or chimeric biomolecules, and within 6 months or 5 half-lives before Visit 1, whichever is longer, until the end of the Follow-up Period. These may include, but is not limited to:
  - Anti-IgE (eg, omalizumab)
  - Anti-IL5 and anti-IL5R (eg, mepolizumab, reslizumab, benralizumab)
  - Anti-IL4R (eg, dupilumab)
- Any immunotherapy within 3 months of Visit 1 up to end of Follow-up, except for stable maintenance dose allergen-specific immunotherapy started at least 4 weeks prior to Visit 1 and expected to continue through to the end of the Follow-up Period.
- Any immunosuppressive therapy (other than systemic corticosteroids) within 3 months of Visit 1 and until the end of the Follow-up Period.
- Any investigational nonbiologic drug within 60 days or 5 half-lives, whichever is longer, prior to Visit 1 and until the end of the Follow-up Period.
- Immunoglobulin or blood products within 4 weeks of Visit 1 until the end of the Follow-up Period.
- Live or attenuated vaccine within 4 weeks of Visit 1 and until the end of the Follow-up Period.
- If a participant is being considered for enrolment into the study and also being considered for COVID-19 vaccination, the participant must not be randomised until at least 30 days after the last dose of vaccine or booster.

Other than the permitted medications, use of concomitant medications or therapies from Screening through to the ETV/end of study is discouraged. Medications or therapies that are

not prohibited and neither compromise participant safety nor affect study data, as judged by the Investigator, will be permitted.

6.6 Intervention After the End of the Study

There are no plans to provide the study intervention, Run-in medications, rescue medication after termination of the study. Participants can return to their usual standard of care medication for their asthma after completion of the study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of Study Intervention for Individual Participants (Part 1 and Part 2)

If any participant meets with any of the following criteria, then he/she will be permanently discontinued from the study intervention.

Part 1

- FEV_1 decrease ≥ 30% from baseline* (as determined by pre first study intervention assessments)
  - In-clinic assessment: Stop dosing and enter participant into Follow-up.
  - Home assessment: Stop dosing and confirm spirometry results in-clinic at earliest opportunity. Enter participant into Follow-up if decline in FEV_1 confirmed (as described in the study reference manual).
  - Characterise potential reasons for the reduction in FEV_1 and determine if consistent with a hypersensitivity-like event, infection, or asthma exacerbation.
  - Participant should be followed until resolution of the symptoms and recovery or stabilisation of FEV_1.

Part 2

- FEV_1 decrease ≥ 30% from baseline*
  - In-clinic assessment: Stop dosing and enter participant into Follow-up:
  - Home assessment: If ≥ 30% decline is sustained over 2 consecutive assessments.
    - Assess associated symptoms and suspend dosing if clinically indicated.
    - Confirm spirometry results in-clinic at earliest opportunity. Enter participant into Follow-up if decline in FEV_1 confirmed.

- If dosing was suspended and if FEV_1 decline is not confirmed, dosing may be resumed at the discretion of the Investigator.
- Characterise potential reasons for the reduction in FEV_1 and determine if consistent with a hypersensitivity-like event, infection, or asthma exacerbation.
- Participant should be followed until resolution of the symptoms and recovery or stabilisation of FEV_1.
- Dosing may be suspended at any time for safety reasons at the discretion of the Investigator.
- Once dosing has been interrupted and resumed, should dosing be suspended again due to safety concerns, the event should be characterised and the patient withdrawn from dosing.

Part 1 and 2

- Withdrawal of consent to further treatment with study intervention.
- Lost to Follow-up.
- Acute severe hypersensitivity or hypersensitivity-like event/anaphylaxis.
- Any TESAE that is considered related to the study intervention by the Investigator.
- Pregnancy.
- Any other AE that, in the opinion of the Investigator or the Sponsor, warrants discontinuation of further dosing of study intervention.
- Haematologic toxicity defined as 1 or more of:
  - Confirmed leucocyte count $< 2.0 \times 10^9$/L.
  - Confirmed neutrophil count $< 1.0 \times 10^9$/L.
  - Confirmed platelet count $< 75 \times 10^9$/L.
  - Confirmed lymphocyte count $< 0.5 \times 10^9$/L.
- Symptomatic bradycardia defined as heart rate < 45 bpm or asymptomatic bradycardia defined as resting supine pulse < 30 bpm while awake persisting for at least 10 minutes.
- Hepatic toxicity defined as 1 or more of:
  - Confirmed ALT or AST increase to > 3 × the ULN.
  - Confirmed isolated TBL increase to > 2 × ULN.
  - Confirmed ALT or AST increase to > 2 × ULN concurrent with an increase in TBL to > 1.5 × ULN.
- A severe asthma exacerbation as defined in Section 8.1.5.
- Confirmed diagnosis of COVID-19 (Part 1 only).
- COVID-19 vaccination** during the study (Part 1 only).

*Baseline Part 1: Mean of Day -1 and Day 1; Baseline Part 2: Mean of Day 1 (15 minutes and 45 minutes pre-dose).

** In Part 1, if the participant is vaccinated during the study, study intervention will be discontinued. The participant will be followed up and included as part of the safety population.

Participants in Part 1 of the study who are permanently discontinued from receiving the study intervention will be followed for protocol specified assessments and follow-up of any AEs as indicated clinically unless consent is withdrawn from further study participation or the participant is lost to Follow-up. Unscheduled assessments for safety may be performed if required. Where possible, participants in Part 1 should follow the PK sampling time frame associated with the last dose as per SoA (Table 1) for Days 28-32 or as directed by the Study Physician. An IPD Visit followed by both follow-up at visits (11 and 28 days after the last study drug intake) may be performed at the Investigator's discretion if visits as per protocol SoA (Table 1) are not required for safety follow-up.

Participants in Part 2 of the study who are permanently discontinued from receiving the study intervention will be followed for any AEs as indicated clinically. This will include performing an IPD Visit as soon as possible after the last study drug intake followed by both follow-up at visit (11 and 28 days) after the last study drug intake unless consent is withdrawn from further study participation or the participant is lost to Follow-up. Unscheduled assessments may be performed in between if required.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

7.1.2 Temporary Interruption of Study Intervention for Individual Participants

7.1.2.1 Dosing Suspension for Individual Participants (Part 1)

- FEV_1 decrease ≥ 20% relative to the prior pre-dose assessment and without recovery to at least 95% of the reference in-clinic assessment prior to the next dose of study intervention during the scheduled residential period
  - Suspend dosing in order to characterise potential reasons for the reduction in FEV_1 and determine if consistent with a hypersensitivity-like event, infection, or asthma exacerbation.
  - Dosing may resume upon recovery of FEV_1 to at least 95% of the reference assessment value and the exclusion of a hypersensitivity-like event, ie, where an alternative explanation is clearly present such as a confirmed upper respiratory tract infection or CRP detection within the normal range.

  - Once the dosing has resumed, should a similar reduction in FEV_1 reoccur, characterise the event and withdraw from dosing.

- FEV_1 decrease ≥ 20% from baseline* sustained until prior to the next dose of study intervention or associated with increased rescue medication use (defined as an increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline** or use of 12 puffs/day or more on any one day), or respiratory AESIs.
  - Suspend dosing in order to characterise potential reasons for the reduction in FEV_1, confirm FEV_1 in-clinic at the earliest opportunity and determine if consistent with a hypersensitivity-like event, infection or asthma exacerbation.
  - Dosing may resume upon resolution of symptoms, stabilisation of rescue medication use and/or recovery of FEV_1 to at least 88% of the baseline value.
  - Once the dosing has resumed, should a similar reduction in FEV_1 reoccur, characterise the event and withdraw from dosing.
- CRP ≥ 10 mg/L plus a moderate AESI (Part 1 only)
  - Reasons for a significant CRP elevation must be investigated.
  - Suspend dosing if accompanied by a moderate AESI.
  - Dosing may resume should the AESI resolve and the reason for CRP elevation attributable to a cause other than AZD1402 eg, confirmed infection and it is considered safe to proceed and no more than 48 hours of the previous dose.
  - Should the CRP ≥ 10 mg/L elevation remain or increase, the new AESIs occur upon resumption of dosing the participant must be withdrawn into the Follow-up.

*Baseline Part 1: Mean Day -1 and Day 1.

**Baseline for rescue medication use defined as the last 7 days of the Run-in Period.

7.1.2.2 Dosing Suspension for Individual Participants (Part 1 and 2)

- Any severe AE or AESI (See Section 8.3.5) with the potential for being classed as a hypersensitivity-like event and not rapidly diagnosed as an infection should result in the suspension of dosing
  - Suspend dosing and fully characterise the event(s).
  - Dosing may resume only in the event of a hypersensitivity-like event being excluded following a full evaluation, including a CRP < 10 mg/L and resolution of the AE(s).

Refer to Section 7.1.1 for further information on FEV_1 30% decline home assessments to inform dosing suspension as per Investigator discretion.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified Follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an ETV should be conducted, as shown in the SoAs (Table 1 and Table 2). See SoAs for data to be collected at the time of study withdrawal and Follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to Follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to Follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoAs (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required will not exceed 500 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Lung Function Test – Spirometry

A centralised spirometry vendor will provide the spirometers and all necessary equipment (computer, calibration syringe, printer, paper, ink, etc.), a detailed study manual, and training to the technicians and Investigator (as needed) in charge of conducting the spirometry for this clinical study. The medications that should be withheld before any pulmonary function tests are mentioned in Section 6.5.3.

Lung function parameters including, but not limited to, FEV_1 and FVC, will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorised delegate according to ATS/ERS guidelines (Miller, et al. 2005).

The vendor providing central spirometry is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate vendor manual. Participants should follow the relevant medication and other restrictions beforehand (Sections 5.1.3 and 5.1.4) If any of the specified restrictions are not met, and the assessment cannot be sufficiently delayed on the day, the assessment should be rescheduled within the allowed visit window.

Time of Day for Scheduled In-clinic Spirometry

Spirometry will be performed at specified timepoints in Part 1 and Part 2 as detailed in the SoAs (Table 1 and Table 2). For all participants, spirometry testing must be initiated between 6:00 AM and 11:00 AM during the Screening, Rescreening, and Run-in Period prior to randomisation. For Part 1, if possible, all post-randomisation morning spirometry assessments should be performed within ± 30 minutes of the time that the randomisation spirometry was performed during the scheduled residential or unscheduled residential period. The evening spirometry should also be performed within a ± 30 minutes window relative to the evening assessment timepoint to ensure the timing of pre-and post-spirometry, study intervention, and controller medication are consistent throughout the residential period. In Part 1 outpatient visits (Day 16, 20, 24, 30 and 32) and visits in Part 2, if possible, all post-randomisation pre-dose morning clinic device spirometry assessments should be performed within ± 1.5 hours of the time that the 15 min prior to randomisation spirometry was performed. For example, if the randomisation spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry Technique

Detailed procedure for performing spirometry will be described in a separate spirometry procedures manual. Details regarding assessment of the quality of spirometry and the BTR (Best Test Report) process will also be detailed in the manual.

At-home Spirometry

During the study period, participants will be required to monitor lung function at home twice daily using an at-home spirometry device. Participants should follow the relevant medication and other restrictions beforehand (Sections 5.3 and 6.5.3). Further details will be provided in a separate instruction manual.

The at-home spirometry device should not be used for decision making purposes and is instead intended to identify declines in lung function that can then be further evaluated (ie, in-clinic spirometry device measurement of lung function, evaluation of symptoms, assessment of key safety laboratory tests).

8.1.2 Reversibility Testing

Airflow reversibility is not an outcome variable. Reversibility testing will be conducted at Visit 1 of Part 2. Participants will need to have a signed ICF prior to the reversibility testing. Participants should be on maintenance ICS-LABA at the time of enrolment (Visit 1), and adhere to medication withhold periods as follows:

(a) SABA and SAMA for at least 6 hours.
(b) Twice daily LABA and/or LAMA-containing therapies for at least 12 hours.
(c) Once daily LABA and/or LAMA-containing therapies for at least 24 hours.
(d) LTRA for at least 24 hours.
(e) Twice daily theophyllines for at least 12 hours.
(f) Once daily theophyllines for at least 24 hours.

For reversibility testing, participants will have a baseline spirometry and a repeat spirometry 15 to 30 minutes after inhalation of 400 µg of salbutamol.

Post-bronchodilator reversibility will be used to determine eligibility only if historical evidence of asthma as per inclusion criteria 16 are not met.

8.1.3 Fractional Exhaled Nitric Oxide

To investigate the effect of AZD1402 on airway inflammation, the measurement of FeNO will be performed in accordance with ATS/ERS guidelines. Standardised conditions with regard to exhalation flow rate and duration of exhalation will be followed such that plateau definition can be evaluated over a minimum of 3 seconds. The concentration of FeNO will be measured in units of ppb. On days when spirometry and FeNO are to be performed on the same day, FeNO measurement should always be carried out prior to spirometry assessments.

Home FeNO will be performed in Part 1. In-clinic FeNO will be performed in Part 1 and 2.

8.1.4 Electronic Diary

At Visit 1 the e-Diary is set up, participants perform training and ACQ-6 is completed. At Visit 2, the participants will receive a handheld e-Diary device to complete during the entire duration of the study. Participants will be provided training on the use of the handheld device. During the study, all participants will be required to take their asthma controller therapy regularly and complete the e-Diary twice daily during the Run-in, Treatment, and Follow-up Period (as per SoA).

Daily assessments will include asthma symptom score (Section 8.1.5), use of rescue medication (Section 8.1.7), CCI [redacted] (Section 8.1.8), FEV_1 data (Section 8.1.1), PEF data (Section 8.1.11), background medication use, and CCI [redacted] use of study intervention.

Participants will also be required to fill in the selected PROs (Section 8.1.10) in the e-Dairy at regular timepoints as indicated in SoAs.

8.1.5 Asthma Exacerbation

During the study, an asthma exacerbation will be defined as a change in the participant's usual asthma symptoms that leads to any of the following:

1 A temporary bolus/burst of systemic corticosteroids for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
2 An emergency room or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above).
3 An in-patient hospitalisation (defined as admission to an in-patient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours).

   A hospitalised asthma exacerbation is defined as any worsening of asthma that leads to (3) above.

Note: For each exacerbation, the criterion/criteria met to confirm exacerbation status should be documented.

Assessment and Documentation of an Asthma Exacerbation

The list below defines what is acceptable documentation for historical exacerbations.

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant was hospitalised/treated with systemic corticosteroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic corticosteroids.
- Evidence of prescriptions for systemic corticosteroids used during an exacerbation.
- A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with corticosteroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

The guidance below defines assessment of asthma exacerbations. The start of an exacerbation is defined as the earliest of the following:

- Start date of systemic corticosteroid background dose.

- Date of emergency room or urgent care visits requiring systemic corticosteroids.
- Date of hospital admission due to asthma.
- The end date of an exacerbation is defined as the latest of the following.
- Last date of systemic corticosteroid dose.
- Date of discharge from emergency room or urgent care visit.
- Date of hospital discharge.
- If < 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation in the statistical analysis.
- All asthma exacerbations that occur during the Treatment Period and Follow-up, must be recorded as an AE in the eCRF.

See Section 8.3.8 for additional information on recording asthma exacerbations as an AE/SAE during the study.

e-Diary Data and Exacerbations

Any sustained increase in asthma symptoms as reported via the e-Diary (or change in background medication that does not meet the definition of criteria of an asthma exacerbation) as defined in the protocol/study reference manual will be graded as a worsening of asthma and will include, but are not limited to:

- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during the Run-in baseline or use of 12 puffs/day on any one day. Systemic steroid use for < 3 days (without hospitalisation ≥ 24 hours). Worsening of asthma should be recorded as AEs in the EDC.

Additionally alerts to the study site to inform AESIs/study stopping/suspension criteria and potential exacerbation/worsening of asthma will also be triggered as defined in the protocol/study reference manual. These may include, but are not limited to:

- FEV_1 decrease ≥ 20% relative to the pre-dose assessment (Part 1 in-clinic assessment only), or
- FEV_1 decrease ≥ 20% compared to baseline (Part 1 home assessment), or
- FEV_1 decrease ≥ 20% compared to baseline (in-clinic assessment), or
- FEV_1 decrease ≥ 30% on 2 consecutive scheduled time points compared to baseline (Part 2 home assessment), or
- Respiratory AESIs* (may include wheeze, cough, shortness of breath), or

- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during the Run-in baseline or use of 12 puffs/day on any one day.

Participants will be required to keep a record of their asthma symptoms in the e-Diary as per the SoAs (Table 1 and Table 2). The applicable data captured in the e-Diary will also be used to determine individuals CCI [redacted] (Section 8.1.12).

* Respiratory symptoms of wheeze, cough and dyspnoea will be reported as alerts in the e-Diary. AESI qualification for reporting purposes are described in Section 8.3.5.

8.1.6 Asthma Symptom Score

Severity scores for asthma symptoms will be recorded twice daily in the morning and evening and documented in the e-Diary during the Run-in, Treatment, and Follow-up Period as per SoAs.

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

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

0: You have no asthma symptoms.

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

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

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

8.1.7 Use of Rescue Medication

Participants will be provided with a SABA as rescue medication, to be used as needed, starting from Visit 1. Participants will be asked to record their daily use of rescue medication in the e-Diary during the Run-in, Treatment, and Follow-up Period. The number of doses of rescue medication (1 dose unit = 1 puff on inhaler) taken will be recorded by the participant in the e-Diary twice daily. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning.

If possible, the rescue medication should be withheld at least 6 hours before any lung function

tests and FeNO measurement.

8.1.8 CCI

CCI [redacted]

8.1.9 Background Medications

Background (ICS and LABA) medication use will be recorded once or twice daily as applicable in the daily e-Diary as "yes" or "no" response.

8.1.10 Participant Reported Outcomes

Participants will be asked to complete the PRO questionnaires on their e-Diary (Section 8.1.4) supplied to the site according to the SoAs (Table 1 and Table 2). The PRO questionnaires to be completed at the site visits must be completed prior to study intervention administration and ideally before any discussions of health status or other study procedures, such as collection of laboratory samples to avoid biasing the participant's responses to the questions. All within-window PRO assessments for the morning and evening assessments at home should be completed within this set time window programmed into the device and will notify the participant when it is time to respond to the questions. A representation of each PRO is included in Appendix H.

Asthma Control Questionnaire-6

The ACQ (Juniper, et al. 1999) was developed to measure asthma control and has been fully validated for use in adults and children 6 to 17 years of age. International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to optimise asthma control (minimisation of symptoms, activity limitation, bronchoconstriction, and rescue bronchodilator use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ was developed to meet these criteria by measuring both the adequacy of asthma control and change in asthma control, which occur either spontaneously or as a result of treatment.

In the ACQ-6, participants will be asked to recall how their asthma has been during the previous week by responding to one bronchodilation use question and 5 symptom questions as follows:

- On average, during the past week, how often were you woken by your asthma during the night?
- On average, during the past week, how bad were your asthma symptoms when you woke up in the morning?

- In general, during the past week, how limited were you in your activities because of your asthma?
- In general, during the past week, how much shortness of breath did you experience because of your asthma?
- In general, during the past week, how much of the time did you wheeze?

Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and scores > 1.5 indicate not well-controlled asthma (Juniper, et al. 2006). Individual changes of at least 0.5 are considered clinically meaningful.

The questionnaire will be completed using the e-Diary in accordance with the SoAs (Table 1and Table 2).

Cough VAS

In Part 1 participants will be asked to complete a cough severity VAS (100 mm linear scale marked with a horizontal line by the participant, with 0 mm representing "no cough" and 100 mm representing "worst cough") measuring subjective assessment by the participant for the prior 24 hours for severity of cough symptoms (Smith, et al 2006)

Study Participant Feedback Questionnaire

This study will include an option for participants to complete an anonymised questionnaire, 'Study Participant Feedback Questionnaire' for participants to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by Investigators. Responses would be used by the Sponsor to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore would not be study data.

8.1.11 Peak Expiratory Flow

Peak expiratory flow will be measured by the participant at home after completing morning and evening e-Diary using a peak flow meter during the Run-in, Treatment Period, and Follow-up Period as per SoAs. Participants will be provided with a device at Visit 2 and receive training on peak flow monitoring at that time.

The morning PEF measurement must be done immediately upon waking up, after the participant has cleared out mucus and before inhaling the study intervention and any rescue medication. The evening measurement should be done just before taking the study intervention. The measurements should be made while standing and the best of 3 attempts. The PEF/FEV_1 data (obtained from the home peak flow meter) will be captured at the

conclusion of the morning and evening e-Diary entry. Participants will have peak flow reviewed at study visits, and can be offered retraining if there are any concerns with the technique.

8.1.12 CCI

CCI

CCI

- CCI
- CCI
- CCI

CCI

CCI

8.2 Safety Assessments

8.2.1 Physical Examinations

- A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the general appearance, skin, abdomen, cardiovascular, and respiratory systems.

Body weight and height will be measured at Visit 1 (Screening) for calculation of body mass index. Participants should be in light indoor clothes without shoes. Body weight will be measured again at Visit 7 and at the last Follow-up Visit.

Physical examination will be performed at timepoints as specified in the SoAs (Table 1 and Table 2).

8.2.2 Vital Signs

Vital signs will be performed at timepoints as specified in the SoAs (Table 1 and Table 2).

The vital signs to be assessed (prior to study intervention administration) are BP (in mmHg) and pulse rate (in bpm), temperature (consistently either oral or tympanic), and respiratory rate measurements.

Systolic and diastolic BP will be measured after at least 5 minutes resting, and before taking any blood sample and conducting any spirometry. Measurements will be carried out with the participant in a seated position and preferably always on the same arm. Data will be recorded on the eCRF.

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

8.2.3 Electrocardiograms

An ECG will be performed at timepoints as specified in the SoAs (Table 1 and Table 2).

Standard digital ECG evaluations will be recorded after approximately 5 minutes resting in supine position and before any blood sampling and spirometry test. Digital ECGs will be recorded by appropriately trained personnel.

The vendor will provide the research sites with the equipment, supplies, specific training, and written instructions.

Following an acquisition of a quality ECG tracing, the Investigator or designee will electronically transfer the data to the vendor.

Individual ECG analysis will be performed by the Investigator at each site. Results will be available on the ECG report printed from the ECG equipment. The responsible Investigator will need to print, date and sign the printed ECG report.

The digital ECG will be recorded at 25 mm/sec and will consist of a recording of leads I, II, III, aVR, aVL, aVF and V1 to V6 and 10 seconds recording of lead II (rhythm strip). At least 3 complete evaluable complexes per lead will be recorded. The following ECG parameters will be determined:

- Heart rate.

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

Individual ECG analysis will be performed by the Investigator at each site. Investigators will assess participants' eligibility according to the ECG report of Visit 1 and Visit 3.

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented and registered in the eCRF.

In case of technical problems, the Investigator considers any result is clinically relevant or doubtful, additional digital ECGs may be performed, using the same equipment, within a reasonable time.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoAs (Table 1 and Table 2). Blood samples should be collected after at least 8-hour fasting at Screening, baseline (prior to first dose of study intervention administration at Visit 3), and Day 28. The results of tests performed at Visit 3 will be regarded as baseline data. Fasting is not required at other timepoints.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

Clinical chemistry, haematology, coagulation, and urinalyses will be analysed centrally. A specific manual will be distributed by the central laboratory.

Local laboratory/on-site assessment of CRP, SARS-CoV-2 PCR, urine cotinine and urine pregnancy tests are described in the SoAs (Table 1 and Table 2).

The following laboratory variables will be measured.

Table 6 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin	SARS-CoV-2 PCR
B-Haematocrit	S/P-Creatinine
B-Erythrocytes	eGFR
B-Reticulocytes (abs, %)	S/P-Bilirubin, total
B-Platelet count	S/P-Alkaline phosphatase
B-Mean corpuscular volume	S/P-Aspartate transaminase
B-Mean corpuscular haemoglobin	S/P-Alanine transaminase
B-Mean corpuscular haemoglobin concentration	S/P-Albumin
B-Red cell distribution width	S/P-Glucose (fasting and non-fasting)
B-Red blood cell morphology	S/P-Cholesterol***
B-Leucocyte count	S/P-Triglycerides***
B-Leukocyte differential count	S/P-C-reactive protein
B-Neutrophils (abs, %)	S/P-Potassium
B-Lymphocytes (abs, %)	S/P-Calcium, total
B-Eosinophils (abs, %)	S/P-Sodium
B-Monocytes (abs, %)	S/P-Creatine kinase
B-Basophils (abs, %)	S/P-high sensitivity C-reactive protein
Urinalysis (dipstick)*	S/P-Direct Bilirubin
U-Haemoglobin/Erythrocytes/Blood	S/P-Indirect Bilirubin (calculation)
U-Protein/Albumin	S/P-Gamma glutamyl transferase
U-Glucose	S/P-Lactate dehydrogenase
U-drug screen**	S/P-Urea nitrogen
U-Specific gravity	S/P-Uric acid
U-pH	S/P-Phosphorus
U-Protein	S/P-Total protein
U-Ketones	S/P-Globulin (calculation)
U-Bilirubin	S/P-Bicarbonate
U-Urobilinogen	S/P-Chloride
U-Nitrite	S/P-Magnesium
U-Leukocyte Esterase	**Coagulation**
Others	International normalised ratio
Hepatitis B Core Total	Activated partial thromboplastin time
Anti Hep B Surface AG2 Qual	Prothrombin time
Hepatitis B – Qual	**Reproductive hormones (Females only)**
Hepatitis B – PCR****	U-human chorionic gonadotropin hormone
Hepatitis C – Virus Antibody	S-human chorionic gonadotropin hormone
Hepatitis C – PCR****	S-Follicle stimulating hormone
HIV 1/2 Ag/Ab Screen	**Safety-Immuno-biomarkers**

Table 6 Laboratory Safety Variables

HIV-1 Ab Supplemental, Geenius	C-reactive protein
HIV-2 Ab Supplemental, Geenius	Immunoglobulins
HIV Ab Interpretation, Geenius	Cytokines*****
HIV Confirmation	Tryptase
QuantiFERON®-TB Gold test	
SARS-CoV-2-serology	
SARS-CoV-2 PCR	

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

NB. In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

The central laboratory will provide the centre with the necessary material and instructions for the sampling. Laboratory data generated will be transmitted to the company in charge of data management activities.

Urine sediment analysis will be performed centrally, only when a positive result in dipstick is obtained. The central laboratory will provide the centres with the necessary material and instructions for urine sampling collection in case sediment analysis is required. Data from the sediment analysis will also be transferred to the company in charge of data management activities.

In addition, details on the collection, processing, shipment of samples and reporting of the results by the central laboratory will be provided to Investigators in the Laboratory Manual.

Safety results will be communicated to the Investigators after each study visit. Investigators must review the lab reports upon receipt, write down the assessment for the abnormal parameters, sign and date them.

8.2.5 Other Safety Assessments

8.2.5.1 Safety Immuno-biomarkers

Blood samples will be collected for immuno-biomarker testing to assess the safety of AZD1402 and per the timepoints mentioned in the SoAs (Table 1 and Table 2) for analysis of immuno-biomarkers including, but not limited to:

- Cytokines, CRP, hs-CRP, and immunoglobulins including IgE.

8.2.5.2 FEV_1

For details on this assessment, refer to Section 8.1.1.

8.2.5.3 FeNO

For details on this assessment, refer to Section 8.1.3.

8.2.5.4 High-resolution Computed Tomography

In the event of respiratory AESIs, FEV_1 decline, or clinically indicated AEs or findings, an HRCT scan of the chest on inspiration may be considered.

8.3 Adverse Events and Serious Adverse Events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF throughout the Treatment Period and including the Follow-up Period.

Serious AEs will be recorded from the time of signing of the ICF.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the Investigator for as long as medically indicated and/or agreed with Sponsor, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE;

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

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to (ie, seriousness criteria)
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The Investigator should assess causal relationship between study intervention and each AE and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events of Special Interest

The following events (occurring after first dose) will be considered to qualify as an AESI for this study.

- $FEV_1 \geq 20\%$ reduction from baseline as informed by in-clinic assessment ("forced expiratory volume decreased")
- $FEV_1 \geq 30\%$ reduction from baseline as informed by
  - in-clinic assessment
  - decline is sustained over 2 scheduled consecutive home assessments resulting in either dosing suspension or discontinuation (Part 2)
- Confirmed fever (> 38°C for > 4 hours)
- Wheeze*
- Cough*
- Dyspnoea/shortness of breath*
- Infection
  - respiratory tract infection, ideally supported by pathogen identification and confirmation
  - COVID-19 infection.
  - non-respiratory tract infection

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

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

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

- SARS-CoV-2 PCR.
- Viral panel which may include, but are not limited to influenza (all types), parainfluenza, respiratory syncytial virus, human metapneumovirus, adenovirus and Bordetella pertussis.
- Mycoplasma pneumonia and Chlamydophila pneumoniae (sometimes included in viral panel).
- Bacterial swab to detect any growth which may include, but are not limited to Streptococcus, Klebsiella, Pneumoniae, Pseudomonas, Staphylococcus aureus, E.coli, Citrobacter, Acinetobacter and Haemophilus influenza.
  The pathogen identification may be performed locally in the first instance, in which case the available tests may differ from those listed. In the event that local laboratory is not used, it may be performed centrally as per standard panel agreed with the Sponsor.

Additionally, CRP ≥ 10 mg/L should be used to support the evaluation and identification of the potential cause of an AESI and to guide further dosing. Unscheduled visit including blood samples collection (including but not limited by haematology, CRP, immuno-biomarkers), local CRP, spirometry, throat swab for pathogen identification, and any other relevant tests which might be required for AE assessment may be requested and scheduled.

8.3.6 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, immuno-biomarkers, and ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, drug interruption).

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

Vital signs, lab abnormalities and ECGs collected at the Screening visit and associated with

pre-existing medical conditions (for example hypertriglyceridemia, elevated glucose, increased BMI) may be reported as medical history if applicable and should not be reported as AEs.

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

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.8 Disease Under Study

The Investigator should report clinically significant worsening of asthma symptoms, including exacerbations, as an AE. Signs and symptoms consistent with a participant's baseline asthma status will not be reported as an AE, unless identified as an AESI.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately (without undue delay), but **no later than 24 hours** of when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately (without undue delay), but **no later than 24 hours** of when he or she becomes aware of it.

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

If the EDC system is not available, then the Investigator or other study site staff reports a SAE

to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the CSP.

The reference document for definition of expectedness/listedness is the IB.

8.3.10 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any study intervention.

8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, AZD1402 should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy.

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 3 weeks following the last dose of study intervention.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 3 weeks after the last dose of study intervention should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.11 Medication Error, Drug Abuse, and Drug Misuse

8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.3.9) and **within 30 days** for all other events.

8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.3.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.12 Medical Device Deficiencies

In this study any deficiency observed with a third-party medical device will be collected and reported to the manufacturer.

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

8.4 Overdose

For guidance refer to AstraZeneca standard operating procedures Reporting of Individual Safety Events in Clinical Studies.

For this study, an overdose is defined as a participant receiving a dose of study intervention in excess of that specified in the IB, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated. The results from future analysis will not be reported in the CSR.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of AZD1402 as specified in the SoAs (Table 1 and Table 2).
- Samples may be collected at additional timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to analyse the PK of AZD1402. Samples collected for analyses of AZD1402 (serum) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.1.1 Part 1

Blood samples for PK assessments will be collected from all the participants at timepoints mentioned in the SoA (Table 1).

8.5.1.2 Part 2

A sparse PK sampling will be carried out for all participants in Part 2 of the study at timepoints mentioned in the SoA (Table 2).

Intense sampling will be performed for a subset of approximately 25% of participants in each treatment arm at timepoints mentioned in the SoA (Table 2). The participants in these subsets may be asked to stay in the clinic overnight for logistical reasons depending on the sampling timepoints.

8.5.1.3 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Placebo samples will not be analysed, unless there is a need to confirm that correct treatment has been given to study participants.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test site operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titre determination. Remaining ADA aliquots will be banked and may be used for further characterisation of the ADA response. The results from these tests will be reported outside of the CSR and full details of the methods used will be described in a separate report. Blood samples for determination of ADA in serum will be collected as specified at timepoints mentioned in the SoAs (Table 1 and Table 2).

Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons.

At the last Follow-up Visit in Part 1 only, if a participant's sample is confirmed ADA positive, the participant will be asked to return to provide another sample to evaluate whether or not ADAs persist.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

Collection of Samples

CCI [redacted]

For storage, re-use and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

- Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoAs.
- CCI [redacted]
- CCI [redacted]
- Blood samples for allergen-specific IgE will be collected for CCI [redacted] and tested in the case of AEs that have characteristics of a type I hypersensitivity-like response.

8.6.2 Collection of Optional Samples for Biomarker Analysis

Collection of optional samples for this part of biomarker analysis is part of this study as specified in the SoAs and is subject to agreement in the ICF addendum.

Blood samples will be collected from participants who have consented to participate in the part of biomarker component of the study. Participation is optional. Participants who do not wish to participate in the optional biomarker research may still participate in the study.

- CCI [redacted]
- CCI [redacted]

For storage, re-use and destruction of biomarker samples, see Section 8.5.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoAs and is subject to agreement in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

CCI

Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No statistical hypotheses will be tested for in Part 1 (Lead-in Cohort) of this study.

Part 2 (Main Cohort) of this study aims to demonstrate that AZD1402 improves FEV_1 compared to placebo.

The null hypotheses for the primary analysis in Part 2 (Main Cohort) are that there is no difference in the change from baseline at Week 4 in FEV_1 in AZD1402 treated participants compared to placebo-treated participants. The following comparisons will be performed:

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

No adjustments for multiple testing will be performed.

9.2 Sample Size Determination

In Part 1 (Lead-in Cohort), approximately 45 participants will be randomised. Part 1a will consist of 30 randomised participants and Part 1b will consist of 15 randomised participants. The sample size for Part 1 (Lead-in Cohort) is not based on any sample size calculation, but was chosen to obtain reasonable evidence of safety and tolerability without exposing undue number of participants to the study intervention. In Part 2 (Main Cohort), 73 evaluable participants per treatment arm will provide CCI % power using a 1-sided test and CCI % significance level to detect a difference of 175 mL in FEV_1 versus placebo. This is based on a

SD of [redacted] mL, derived from an inter-participant SD of [redacted] mL in change from baseline to Week 4, adjusted for 4 repeated measurements and a correlation of [redacted] between weekly measurements. Assuming a dropout rate of [redacted]%, approximately 80 evaluable participants per arm are needed. Due to the restricted recruitment into the [redacted] mg dose arm the precision of inference in terms of statistical power will be less than [redacted]% for the comparisons [redacted] mg versus placebo. A participant will be considered evaluable if he/she has baseline and Week 4 FEV_1 results available.

Part 2 will consist of approximately 165 participants.

9.3 Populations for Analyses

The following populations are defined:

Table 7 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the informed consent form.
Full Analysis Set (FAS)	All participants who are randomised and received any study intervention. Participants are evaluated according to the treatment assigned at randomisation. The FAS will be used for all analyses of demographic baseline characteristics and efficacy data.
Per Protocol Set (PPS)	A subset of the FAS consisting of all participants who do not violate the terms of the protocol in a way that may affect the primary efficacy endpoint significantly. All decisions to exclude participants from the PPS will be made and documented prior to the unblinding of the study.
Safety Set (SS)	All participants who are randomised and received any study intervention. Participants are evaluated according to the actual treatment they received. If a participant received a different treatment dose than randomised throughout the study, they will be analysed according to treated dose, not the randomised dose. If a participant received study intervention from the wrong kit for only part of the treatment duration, they will be analysed according to their randomised dose. The SS will be used for all safety analyses.
Pharmacokinetic (PK) set	All participants in the SS who have detectable PK data and with no major protocol deviations considered to impact on the analysis of PK data. The exclusion of any participants or timepoints from the calculation of the PK parameters will be documented by the PK scientist including the reason(s) for exclusion prior to the unblinding of the study. The available concentration data and PK parameter data for any participants excluded from the PK analysis set will be listed only, and presented in the individual figures of concentration-time plots. The PK analysis set will be used for all PK analyses.
Immunogenicity set	All participants in the SS with at least one post-treatment ADA result (positive or negative) with exception for any analysis of relationship of

Population/Analysis set	Description
	ADA with PK where the immunogenicity set will instead include all participants in the PK set. The immunogenicity analysis set will be used for all ADA analyses.

Abbreviations: ADA = anti-drug antibody; FAS = full analysis set; PPS = per protocol set; PK = pharmacokinetics; SS =safety set

Additional analysis sets may be defined in the Statistical Analysis Plan (SAP) for exploratory analyses.

9.4 Statistical Analyses

The SAP will be finalised prior to first participant in and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Statistical Considerations

Analyses will be performed by Parexel, except for the derivation of PK parameters, which will be performed by bioanalytical test sites operated on behalf of AstraZeneca Research and Development.

Continuous data will be summarised using descriptive statistics (number of observations, mean, SD, median, 25th and 75th percentiles [where appropriate], minimum and maximum). For log-transformed data (where appropriate) geometric mean and geometric coefficient of variation will also be presented. For PK data, geometric +SD and geometric -SD are also presented in addition to geometric mean and geometric coefficient of variation. Frequencies and percentages will be used for summarising categorical (discrete) data.

Confidence intervals will generally be 2-sided with 95% confidence level, and p-values will be one-sided, unless otherwise indicated.

Unless otherwise stated, summaries will be presented by Part and treatment. The treatment comparisons of interest are the different doses of AZD1402 versus placebo. No formal comparisons between the different AZD1402 doses will be conducted.

All statistical analyses will be conducted using SAS® version 9.4.

Deviations from the protocol will be assessed as “important” or “not-important”. Important deviations from the protocol may lead to the exclusion of participants from any of the study analysis set. Deviations will be defined before database hard lock. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria.
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.
- Receiving incorrect study intervention than randomised to.

All protocol deviations will be discussed at a data review meeting prior to database hard lock in order to define the analysis sets for the study. All important protocol deviations will be listed by participant. Further details will be provided in the SAP.

9.4.2 Efficacy – Part 2

The analysis of all efficacy variables will be performed on the FAS.

9.4.2.1 Primary Endpoint

The primary efficacy endpoint for Part 2 (Main Cohort) is the change from baseline in pre-bronchodilator FEV_1 at Week 4 compared to placebo.

The change from baseline in FEV_1 will be analysed using MMRM with treatment group, week (1 to 4), country, eosinophil count group (< 300, ≥ 300 cells/μL), baseline FEV_1, and treatment-by-week interaction as fixed effects with participant as random effect. In this model, Week 1 to 4 corresponds to Visit 4 to 7. The within-participant correlation will be modelled using the unstructured covariance matrix. The Kenward-Roger approximation will be used to estimate the degrees of freedom.

Baseline for FEV_1 will be defined as the mean of the 2 measured values before first study intervention administration (30 minutes apart, at -45 minutes and -15 minutes, before study intervention) on Day 1.

Besides the main analysis in the FAS, treatment effect in primary endpoint will be evaluated in subgroups defined by measurements of eosinophil count (< 300 and ≥ 300 cells/μL), and of FeNO (< 50 and ≥ 50 ppb) evaluated at Day 1 pre-dose.

9.4.2.2 Secondary Endpoints

Secondary efficacy endpoints for Part 2 (Main Cohort) will include:

- Change from baseline in pre-bronchodilator FEV_1 average over the 4-week Treatment Period
- Change from baseline in ACQ-6 at Week 4 and average over the Time Period
- Change from baseline in average morning PEF over the Treatment Period
- Change from baseline average evening PEF over the Treatment Period

- Change from baseline in daily average asthma symptoms score (AM/PM) over the Treatment Period
- Change from baseline in FeNO at Week 4 and average over the Treatment Period (analysed on natural log scale and results back transformed to linear scale).

Similar MMRM as for the primary variable will be used for analysis of change from baseline in ACQ-6 and in FeNO. Analysis of covariance with treatment and country as fixed effects, and baseline as covariate will be used for the analysis of change from baseline in average PEF.

Further details on the models for secondary endpoints will be provided in the SAP.

9.4.2.3 Exploratory Endpoints

CCI [redacted]

Analyses of exploratory endpoints for Part 2 (Main Cohort) will be specified in the SAP.

9.4.3 Safety

Safety analysis will be performed using the SS. Individual safety and tolerability data will be provided in data listings and summarised as appropriate by treatment and overall, separate for each part.

Further details on the analysis of safety data will be described in the SAP.

9.4.3.1 Adverse Events

Adverse events will be coded using the most recent version of the MedDRA.

Adverse events will be presented separate for each Part by treatment, SOC and/or PT presenting number and percentage of participants reporting at least one event. Number of events will be presented separately.

Only AEs occurring with an onset date, or worsening, on or after first dose of study intervention will be presented in summary tables. Adverse events occurring prior the first dose of study intervention will be included in data listings.

An overview of AEs will be presented for each Part and treatment. The presentation will include the number and percentage of participants with any AE, AEs with outcome of death, SAEs, AEs leading to discontinuation of study intervention, AEs leading to withdrawal from study, and AEs of special interest (including infection, eosinophilia, and hypersensitivity events) as well as the number of individual occurrences in those categories.

An additional table will present the number and percentage of participants with most common AEs. Most common (eg, frequency of >5%) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants in any treatment group.

Key participant information will be presented for participants with SAEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention.

An AE listing for the SS will cover details for each individual AE; an AE listing for participants who were not exposed to study intervention will be presented separately.

Full details of the AE analyses will be provided in the SAP.

9.4.3.2 Deaths

Details on deaths will be listed by participant.

9.4.3.3 Exposure

Details on study intervention administration will be provided in listings and will be summarised descriptively.

9.4.3.4 Vital Signs

Vital sign parameters will be presented separately for each Part by treatment using descriptive statistics.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and changes from baseline.

9.4.3.5 Laboratory Parameters

Laboratory parameters will be presented separately for each Part by treatment using descriptive statistics.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry, haematology, and coagulation parameters will be presented for observed values and changes from baseline.

Elevation in liver parameters for assessment of Hy's Law will be done and reported appropriately if potential cases have been identified during the course of the study.

Shift tables will present the baseline assessment against the maximum on-treatment results.

9.4.3.6 Immuno-biomarkers

Results on immuno-biomarkers (cytokines, CRP, and immunoglobulins including IgE) will be

presented descriptively by treatment, separately for each part.

9.4.3.7 Electrocardiogram

Descriptive statistics will be produced at each scheduled assessment timepoint for all quantitative ECG parameters for both absolute values and changes from baseline.

An analysis of potentially clinically significant ECG values on QT, QTcB, QTcF, QRS and PR interval and heart rate will be performed. The number of participants with potentially clinically significant ECG values will be tabulated across time and treatment. The criteria based on severity will be defined in the SAP.

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

- Absolute value > 450 msec
- Absolute value > 480 msec
- Absolute value > 500 msec
- Increase from baseline > 30 msec
- Increase from baseline > 60 msec

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

Pharmacokinetic analysis for AZD1402 will be performed by PK analysis vendor on behalf of AstraZeneca Research and Development. Pharmacokinetic parameters will be derived using standard non-compartmental methods using Phoenix® WinNonLin® version 8.1 or higher (Certara). All descriptive statistics will be performed using SAS® version 9.4.

The PK parameters will be calculated/estimated according to AstraZeneca standards.

Pharmacokinetics analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations.

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

Cmax	Maximum observed serum (peak) drug concentration
tmax	Time to reach peak or maximum observed concentration or response following drug administration
Ctrough	Observed lowest drug concentration reached before the next dose is administered (pre-dose)
λz	Terminal rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
t1/2λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
AUClast	Area under the serum concentration-curve from zero to the last quantifiable concentration
AUCτ	Area under serum concentration-time curve in the dosing interval τ
CL/F	Apparent total body clearance of drug from serum after extravascular administration
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)
Dose normalised AUCτ	Area under the serum concentration-time curve in the dosing interval τ divided by the dose administered
Dose normalised Cmax	Maximum observed serum (peak) drug concentration divided by the dose administered
Dose normalised AUClast	Area under the serum concentration-time curve from zero to the last quantifiable concentration divided by the dose delivered in mg
tlast	Time of last observed (quantifiable) serum concentration
Rac AUC	Accumulation ratio for AUCτ
Rac Cmax	Accumulation ratio for Cmax

The following diagnostic parameters for PK analysis will be provided:

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

Additional PK parameters may be determined where appropriate.

Serum concentrations will be listed and summarised by treatment and PK day using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric coefficient of variation, geometric mean +geometric standard deviation, geometric mean –geometric standard deviation, arithmetic mean, arithmetic SD, median, minimum and maximum based on the PK analysis set. Serum concentrations that are BLQ will be handled as described in the SAP.

Combined individual serum concentration per dose level and PK day (spaghetti plots) will be presented in linear and semi-logarithmic scale with separate plots for each dose level and PK day. Figures for the geometric mean concentration-time data will be presented for all doses overlaid on the same plot for a given PK day, in both a linear and semi-logarithmic scale.

Figures for the geometric mean concentration-time data will also be presented for PK Days 1 and 28 overlaid on the same plot for a given dose level, in both a linear and semi-logarithmic scale.

Individual Ctrough values will be plotted versus study day, in linear and semi-logarithmic scale for each dose level and PK day. Figures for geometric mean Ctrough versus study day will be presented for all doses and study days overlaid on the same plot, in both linear and semi-logarithmic scales.

All serum PK parameters will be listed for each participant and summarised by treatment and PK day using similar descriptive statistics.

Further details regarding the calculation and descriptive statistics of the PK parameters will be detailed in the SAP.

9.4.4.2 Immunogenicity

Immunogenicity results will be presented descriptively, separately for each Part.

Participants will be classified as ADA positive or ADA negative. ADA-positive results will further be classified on whether positivity was observed during the 4-week Treatment Period or after the 4-week Treatment Period. Pharmacokinetic and safety profiles will be presented graphically for ADA-positive participants with onset during the 4-week Treatment Period, ADA-positive participants with onset after the 4-week Treatment Period and ADA-negative participants. Similarly, tabular presentation for AEs across the 3 ADA groups will also be presented. Further details will be provided in the SAP.

9.5 Interim Analyses

An interim analysis of the primary endpoint (FEV_1) may be performed. The main objective of this analysis is to estimate the variability for a sample-size re-estimation or perform a futility analysis. The timing of the interim analysis is to be determined such that the estimated variability enables an informative decision on whether to revise the sample size. Decision criteria will be pre-specified in an interim analysis plan (charter). Depending on the outcome of the interim analysis, the sample size may be increased from 80 up to 107 per arm ([redacted] mg dose and placebo) in Part 2.

9.6 Data Monitoring Committees

The SRC including the Sponsor study team will review PK and unblinded safety data

following completion of Part 1a before progressing to Part 1b/2 and following completion of Part 1b. An unscheduled SRC meeting may also be held in the event of any safety or tolerability events requiring further review that may impact continuation of a cohort or the study, including unblinding data as required.

A DSMB will oversee Part 2 of the study and review the unblinded interim outputs. In addition to a full DSMB periodic review of safety data, the committee can meet on an ad hoc basis, eg, in the event of any potential suspension or stopping criteria for dose level or study being met. Details of the composition of the DSMB, frequency of meetings and remit can be found in the DSMB Charter.

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

The finalized version of the charter will be submitted to regulatory and ethics authorities (as appropriate/per local requirements) once complete, once data from Part 1 are available and prior to inclusion of the first patient in Part 2 of the study.

For details on the SRC, DSMB, and URC, refer to Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and Investigators.
- For all studies except those utilising medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

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

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A 5.1 Data Safety Monitoring Board

In order to provide a periodic review of safety throughout the study, in addition to the ongoing, blinded review provided by the Sponsor/Designee Medical Monitor for detection of any potential safety signals, an unblinded DSMB will be utilised. Set up of the DSMB, and frequency of data transfer will be described in the DSMB Charter. The DSMB will make any necessary recommendations regarding further conduct of the study based on their evaluation of emerging data.

A 5.2 Safety Review Committee

This study will convene an unblinded SRC whose membership and remit will be detailed in the SRC charter and may include the Sponsor study team and the Study Physician, to review unblinded safety and PK data at the following timepoints:

- After completion of Part 1a treatment period, prior to starting Part 1b and Part 2.
- Following completion of Part 1b treatment period.
- An unscheduled SRC meeting (as detailed in the SRC Charter) in the event of any safety or tolerability events requiring further review that may impact continuation of a cohort or the study, including unblinding data as required.

A 5.3 Unblinded Review Committee

The URC is a committee internal to AstraZeneca and responsible for reviewing interim data from trials and accountable for ensuring each review is done in a way that maintains the scientific integrity of the trial.

Details regarding each of these committees will be made available in their respective charters.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU Clinical Trials Information System within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study reference manual.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study archiving, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in source data agreement and computerised data check list for electronic source data.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a participant or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including Run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, Run-in, Treatment, Follow-up), that fulfils one or more of the following criteria:

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

Adverse events for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outparticipant treatment in an emergency room is not in itself an serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a

causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)

- Participant failed to return unused medication or empty packaging

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole

- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy Volunteers and paediatric participant samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at Visit 3 after randomisation. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The recommended default storage time is 15 years; this may vary in different territories. In some circumstances, there may be a rationale for the storage of DNA samples until they are depleted. When defining the storage time local laws and regulations for the storage of genetic samples must be considered.
- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study, the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Investigator is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participant, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report PHL cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law
Aspartate Aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2× ULN at any point during the study following the start of study intervention irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law
Aspartate Aminotransferase or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the

same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting study intervention, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's Law lab kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

[#]**A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether

there is an alternative explanation for meeting PHL criteria other than DILI caused by the study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to study intervention and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and

amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a]HBV DNA is only recommended when IgG anti-HBc is positive
[b]HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c]CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

E 7 References

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, et al. Case definition and phenotype standardization in drug-induced liver injury.2011, Clinical Pharmacology and Therapeutics 2011, 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-

guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F COVID-19 Specifics

F 1 Background to COVID-19

There is currently an outbreak of respiratory disease (COVID-19) caused by a novel SARS-CoV-2 that was first detected in Wuhan City, Hubei Province, China in 2019. This new virus has rapidly spread across the globe causing the WHO to declare a pandemic situation on 12 March 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect participants, site staff, and society as a whole.

Both EMA and FDA as well as national health authorities in Europe have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued EMA guideline.

F 2 Risk Assessment for COVID-19 Pandemic

The study intervention and its mechanism of action is unlikely to impact on the course of infection with SARS-CoV-2. AZD1402 administration results in blockade of IL-4α that could result in increased susceptibility to lung infections in general, but the risk of susceptibility to SARS-CoV-2 is unknown. The risk of exposure to infected people cannot be completely excluded as the participants may need to be in public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

Measures to mitigate the additional risks caused by COVID-19 are:

- Participant specific inclusion and exclusion criteria:
  - Exclusion of patients with active COVID-19 infection or significant respiratory disease (other than asthma)
  - Exclusion of participants with a diagnosis of / suspected COVID-19 infection with associated pneumonia / pneumonitis as described in Section 5.2.
- This study is going to start enrolling only when the Sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local

confinement measures or other safety restrictions linked to the COVID-19 pandemic imposed by the local authorities are compatible with safe conduct of the study.

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
- Participants will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnoea, sore throat, and fatigue throughout the study during the pandemic. Once clinical signs of infection are reported by participants, the Investigator needs to determine whether samples can be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. The decision to continue with dosing the participant with the study intervention in the event of him/her showing symptoms of COVID-19 infection will be per Investigator's discretion.
- The probability of virus transmission will be controlled as much as possible by:
  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests, logistical aspects of travel/test site, and on Investigator's discretion.
  - Requesting all participants are contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, participants are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, participants will be referred to the local health care system for further follow-up and treatment.
  - Physical distancing and person-to-person contact restrictions will be applied during site visits.
  - Where physical distancing is not possible, personal protective equipment will be used by study participants (surgical face mask, gloves) and staff (for example but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the Investigators and site staff and guided by local requirements.
  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.
  - If, for reasons related to the COVID-19 pandemic (eg, local lockdown, self-isolation requirements), a participant is not able to attend their scheduled visit within the visit window, they can have their visit rescheduled as detailed in the study reference manual/as per agreement with the Sponsor study physician. Where visits cannot be rescheduled, participants should continue at the next scheduled visit. Additionally, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow collection

of data for AEs, concomitant medications, adherence to the e-Diary and PRO measures to be reported and documented. The term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

- If site visits are not possible due to local restrictions, home nursing visits may be considered after discussion with and approval by the Sponsor according to local regulations. The Principal Investigator will be responsible to delegate any study procedure, however the Principal Investigator will retain responsibility for evaluation of the data collected. In all cases, informed consent should always be collected in writing.

F 3 Restrictions Related to COVID-19

During the COVID-19 pandemic, participants are advised to adhere to local requirements for reduction of the public SARS-CoV-2 exposure while ambulatory. If applicable, prior to Screening (Visit 1), potential participants should be called to confirm they are not experiencing any COVID-19 symptoms and signs and are asked not to attend the site in case of suspected infection. If appropriate, participants will be referred to the local health care system. Physical distancing and person-to-person contact restrictions will be applied and explained to participants while staying at the study site. Where physical distancing is not possible, study participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the Investigator and site staff and guided by local requirements.

F 4 Data Quality Assurance Related to COVID-19

Monitoring visits at site will be limited to a minimum required as deemed appropriate during COVID-19 pandemic, per local regulations.

In addition, where possible, other measures for carrying out protocol related activities, such as but not limited to home nursing, may be employed as required.

F 5 References

- Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, EMA, Version 4 (04/02/2021). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
- Supplementary recommendations of BfArM and PEI to the European Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, version 4 (2021.05.06). https://www.bfarm.de/EN/Drugs/licensing/clinicalTrials/news/CT_COVID19.html

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, March 2020, Updated on June 03, 2020 https://www.fda.gov/regulatoryinformation/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medicalproducts-during-covid-19-public-health-emergency.

Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

G 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained where applicable, and where consent has not already been provided for the alternative means of carrying out visits and assessments. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The Investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IMP. If this delay is outside the screening window specified in Table 1 and Table 2, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Table 1 and Table 2. The procedures detailed in Section 5.1 and Section 5.2 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

G 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the participants home/or other remote location as per local SOPs/local regulations, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP. Home visits may be combined with telemedicine visits.

G 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines and where a home or remote visit is not possible. Having a telemedicine contact with the participants will allow collection of AEs, concomitant medication, adherence to the e-Diary and PRO measures to be reported and documented, and any information that may be possible to collect virtually.

G 5 At-home or Remote Location IMP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IMP may be performed where this is not already specified in the protocol. The option of at-home or remote location IMP administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IMP administration during other study disruptions, eg, site closures due to natural disaster.

G 6 At-home or Remote Location IMP Administration by the Participant

Prior to at-home or remote location IMP administration outside the scope of the protocol, the Investigator must assess the participant or his/her caregiver to determine whether they are appropriate for continued at-home or remote location administration of IMP. All necessary supplies and instructions for administration and documentation of continued home IMP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

G 7 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

Appendix H Patient-reported Outcomes

H 1 Asthma Control Questionnaire-6

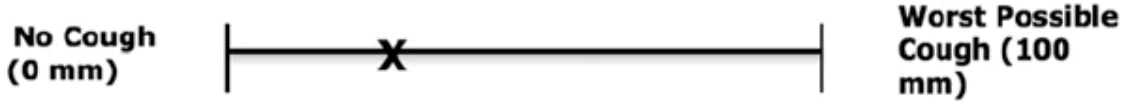
Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1.	On average, during the past week, how often were you **woken by your asthma** during the night?	0 Never 1 Hardly ever 2 A few times 3 Several times 4 Many times 5 A great many times 6 Unable to sleep because of asthma
2.	On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?	0 No symptoms 1 Very mild symptoms 2 Mild symptoms 3 Moderate symptoms 4 Quite severe symptoms 5 Severe symptoms 6 Very severe symptoms
3.	In general, during the past week, how **limited were you in your activities** because of your asthma?	0 Not limited at all 1 Very slightly limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Totally limited
4.	In general, during the past week, how much **shortness of breath** did you experience because of your asthma?	0 None 1 A very little 2 A little 3 A moderate amount 4 Quite a lot 5 A great deal 6 A very great deal

5.	In general, during the past week, how much of the time did you **wheeze?**	0 1 2 3 4 5 6	Not at all Hardly any of the time A little of the time A moderate amount of the time A lot of the time Most of the time All the time
6.	On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0 1 2 3 4 5 6	None 1 - 2 puffs/inhalations most days 3 - 4 puffs/inhalations most days 5 - 8 puffs/inhalations most days 9 - 12 puffs/inhalations most days 13 - 16 puffs/inhalations most days More than 16 puffs/inhalations most days

H 2 Cough VAS



H 3 SPFQ

There will be 3 optional questionnaires for participant completion at Run-in (Visit 2), during the Treatment Period (Visit 3 in Part 1 and Visit 5 in Part 2), and at end of the study (Follow-up Visit 11 in Part 1 and Follow-up Visit 9 in Part 2, or ETV).

A. SPFQ at Run-in

Your experience before you started the study: to be completed within 28 days prior to randomisation

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
A1. I understand the treatment process in this trial (for example: when and how to take or use a treatment)	0	1	2	3	4
A2. The information given to me before I joined the trial was everything I wanted to know (for example: visits and procedures, time commitment, who to contact with questions)					
A3. The information given to me before I joined the trial was easy for me to understand (for example: visits and procedures, time commitment, who to contact with questions)					
A4. I felt comfortable that I could ask any questions before I joined the trial					

B. SPFQ during the Treatment Period

Your experience during the study: to be completed during the Treatment Period

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
B1. Overall I am satisfied with the trial site (for example: comfort and privacy of treatment area, waiting area, parking, ease of access to the site)	0	1	2	3	4
B2. My trial visits have been well organized					
B3. My trial visits are scheduled at a convenient time for me					
B4. The staff treats me with respect					
B5. I feel comfortable that I can ask questions during the trial					
B6. I am satisfied with the answers I have received to my questions during the trial					
	No		Yes		
B7. The time taken to collect data is acceptable to me (for example: in person visits, questionnaires, forms)					
B8. The impact the trial has on my daily activities is acceptable (for example: household chores, work commitments, eating)					

C. SPFQ at the end of the study participation

Your experience at the end of the study: to be completed at last Follow-up Visit or ETV

Please select **one** response for each item.	No		Yes		
C1. I was informed when I had completed the trial					
C2. I was informed of any future opportunities to access the overall trial results if I wanted to					
	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
C3. Overall, I was satisfied with the information I received about future support after the trial (for example: future treatment, follow-up contact details)	0	1	2	3	4
C4. Overall, I was satisfied with my trial experience					
	Much less than expected	Somewhat less than expected	Same as expected	Somewhat more than expected	Much more than expected
C5. Compared to when the trial started, the overall commitment required was similar to what I expected	0	1	2	3	4

Appendix I Definitions, Management and Classifications of Hypersensitivity Reactions

National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Dispenza MC. Classification of Hypersensitivity reactions. Allergy Asthma Proc 2019 40:470-473.

Appendix J Abbreviations

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire-6
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AM	before noon (ante meridiem)
AST	aspartate aminotransferase/transaminase
ATS	American Thoracic Society
BID	twice daily
BP	blood pressure
bpm	beats per minute
CAPA	Corrective and Preventative Action
COPD	chronic pulmonary obstructive disease
COVID-19	Coronavirus disease-2019
CRP	C-reactive protein
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DPI	dry powder inhaler
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ERS	European Respiratory Society
ETV	early termination visit
EU-CTR	European Union Clinical Trial Regulation
FAS	full analysis set
FDA	United States Food and Drug Administration

Abbreviation or special term	Explanation
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in one second
FSH	follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCP	Health Care Professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hy's Law
CCI	CCI
hs-CRP	high-sensitivity CRP
CCI	CCI
HR	heart rate
HRCT	high-resolution computed tomography
HRT	hormone replacement therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IPD	Intervention Discontinuation Visit
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon gamma release assay
IL	interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	long-acting beta-adrenoceptor agonist
LAMA	long-acting muscarinic antagonist

Abbreviation or special term	Explanation
LTRA	leukotriene receptor antagonists
MART	Maintenance and Reliever Therapy
MMRM	mixed model repeated measure
MedDRA	Medical Dictionary for Regulatory Activities
MDI	multiple dose inhaler
NIMP	Non-investigational medicinal product
NYHA	New York Heart Association Score
NGAL	neutrophil gelatinase-associated lipocalin
OCS	oral corticosteroids
CCI	CCI
PCR	polymerase chain reaction
PD	pharmacodynamics
PHL	potential Hy's Law
PEF	peak expiratory flow
PM	after noon (post meridiem)
PPS	per protocol set
ppb	part per billion
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PT	preferred term
QT	QT interval
QTcF	QT interval corrected using Fridericia's formula
QTcB	QT interval corrected using Bazett's formula
QRS	QRS interval
RNA	ribonucleic acid
RR	RR interval
RTSM	Randomisation and Trial Supply Management
SABA	short-acting beta agonist
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAMA	short-acting muscarinic antagonist
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SoA	Schedule of Activities

Abbreviation or special term	Explanation
SPFQ	Study Participant Feedback Questionnaire
SOC	system organ class
SOP	Standard Operating Procedures
SRC	Safety Review Committee
SS	safety set
TB	tuberculosis
TBL	total bilirubin
Th2	T helper cell type 2
Tlc	tear lipocalin
TPV	Third-party Vendor
ULN	upper limit of normal
URC	Unblinded Review Committee
VAS	Visual Analogue Scale

Appendix K Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1: 23 November 2020

Overall Rationale for the Amendment

The original Clinical Study Protocol (CSP), Final 1.0, dated 20 October 2020, was updated to:

- Clarify Safety Review Committee (SRC) requirements, stratification, sampling, and medical device deficiencies for clarity and completeness.
- Add study mitigation language which will provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with Good Clinical Practice (GCP), and minimizing risks to the study integrity.
- Clarify some study procedures.
- Make minor editorial updates throughout.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Section 4.1.1 Part 1	Additional description that data will be unblinded for SRC review, but study participants will remain blinded	Additional clarification on unblinding of data for SRC review	Non-substantial
	Update of stratification for Part 1 of the study to stratification by site in Australia and New Zealand	Update made for logistical reasons	Substantial
Section 1.1 Synopsis, Section 4.1.1 Part 1, Section 9.6 Data Monitoring Committees, Appendix A 5.2 Safety Review Committee	Addition of unscheduled SRC meeting	To allow for an unscheduled SRC meeting in the event of any safety or tolerability events requiring further review that may impact continuation of a cohort or the study	Substantial
Section 1.3 Schedule of Activities	CCI [redacted]	CCI [redacted]	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	CCI [redacted]	Added for clarification	Non-substantial
	Addition/revision of footnote to clarify timing of in-clinic outpatient visits and timing of vital sign measurements.	Added for clarification	Non-substantial
Section 4.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.	Substantial
Section 6.1.1 Investigational Products	Update of dosage levels for placebo to "NA"	Updated to match the unit dose strength as there are no dose levels of placebo	Non-substantial
Section 8.3.2 Follow-up of AEs and SAEs Section 8.6.1 Collection of Mandatory Samples for Biomarker Analysis	Removal of blood samples for complement testing	Test will not clearly inform safety or scientific data	Substantial
Section 8.3.12 Medical Device Deficiencies	Removal of the sentence "The manufacturers medical device complaint report will be used to collect the deficiency."	Collection of deficiencies and reporting to third party is already stated, this level of detail is not required in the protocol	Non-substantial
Section 8.6.2 Collection of Optional Samples	Removal of genomics initiative sample from this section	To allow for two separate samples to simplify optional consent	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
for Biomarker Analysis			
Appendix A 5.2 Safety Review Committee	Removal of "independent" from and addition of PK data to the unblinded SRC review	To clarify protocol inconsistency in SRC data review description	Non-substantial

Amendment 2: 10 March 2021

Overall Rationale for the Amendment

The Clinical Study Protocol (CSP), Final 2.0, dated 23 November 2020, was updated to increase flexibility in assessments, increase clarity, and to account for COVID-19 vaccination. Numerous other minor editorial updates also made throughout.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis Section 4.1.2 Part 2	Randomisation strategy of 2:1 (active to placebo) added for Part 2	For clarity on randomisation strategy	Non-substantial
Section 1.3 Schedule of Activities	Order and timings of home device versus clinical spirometry updated	For flexibility in assessments and to increase clarity	Non-substantial
	Urine pregnancy test for Part 1 of the study moved to Day -1	To decrease the number of tests required on dosing day	Non-substantial
	Collection windows for clinical spirometry and timing of clinical spirometry relative to randomisation spirometry specified	For flexibility in assessments and to increase clarity	Non-substantial
	Statement added to allow order of assessments to be updated in consultation with the Sponsor study physician	For flexibility in assessments	Non-substantial
	Vital sign collection times updated	For flexibility in assessments and to increase clarity	Non-substantial
	Collection windows updated for electrocardiogram collection	For flexibility in assessments and to increase clarity	Non-substantial
	Pharmacokinetic sampling windows updated	For flexibility in assessments and to increase clarity	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Blood sample collection timepoint for IgE updated to Day -1 or Day 1 pre-dose	For logistical reasons	Non-substantial
	Collection timepoint for optional samples updated	For flexibility in assessments	Non-substantial
	Additional urine pregnancy test collection timepoints added to Part 2	To cover duration of study participation	Non-substantial
Section 1.3 Schedule of Activities Section 4.1.1 Part 1 Section 4.1.2 Part 2 Section 6.1.3.3 Treatment Period	Dosing interval for study intervention/placebo updated to [redacted]	To clarify the required time windows	Non-substantial
Section 1.1 Synopsis Section 4.1.1 Part 1	Stratification by site for randomization updated to replace New Zealand with Germany	To reflect updated country selection.	Non-substantial
Section 4.1.1 Part 1	Figure 3 updated to correct typo in Part 1a [redacted] mg (DPI/DPI corrected to DPI/[redacted])	To fix typo	Non-substantial
Section 4.4.1 Premature Termination of the Study and Stopping Criteria	Update to pharmacokinetic stopping criteria	The Phase I peak concentration and exposure limits, which included a 3-fold safety factor, have been updated for Phase IIa to match the observed values achieved at the no-observed-adverse-effect-level (total AZD1402 assay) in the 4-week humanised mouse toxicology study (matching the duration of the Phase IIa study).	Substantial
Section 5.1 Inclusion Criteria	Contraception requirements updated for male participants	To accommodate countries where spermicides are not available	Non-substantial
Section 5.2 Exclusion Criteria	Exclusion criterion added regarding receipt of COVID-19 vaccination	Criterion added to address any potential safety concerns and/or interpretation of data as a result of COVID-19 vaccination	Substantial
Section 6.5.4 Restricted and	Enrolment requirements for participants receiving	Added to clarify prohibited medication in relation to COVID-19 vaccination in order to	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Prohibited Medications	COVID-19 vaccination added	address any potential safety concerns and/or interpretation of data as a result of vaccination	
Section 7.1.1 Permanent Discontinuation of Study Intervention for Individual Participants (Part 1 and Part 2)	Withdrawal criteria related to COVID-19 vaccination added	Criterion added to address any potential safety concerns and/or interpretation of data as a result of COVID-19 vaccination	Substantial
Section 8.1.1 Lung Function Test – Spirometry	Specified that it is post-randomisation clinical device spirometry that should be performed within ± 1.5 hrs of the time that randomisation spirometry was performed	For clarity alignment with changes made to Section 1.3	Non-substantial
Section 8.1.4 Electronic Diary Section 8.1.6 Asthma Symptom Score Section 8.1.7 Use of Rescue Medication Section 8.1.8 CCI [redacted]	Specified the periods wherein the eDiary needs to be completed	Clarification of inconsistency in the time period for eDiary completion	Non-substantial
Section 8.1.11 Peak Expiratory Flow	Timing of evening measurement updated from " just before going to bed" to CCI [redacted]	To clarify inconsistency and timing of PEF measurement timing in relation to study intervention	Non-substantial
Section 8.2.2 Vital Signs	Requirement for temperature measurement to be consistently oral or tympanic added	To ensure consistency of measurement method	Non-substantial
Section 8.2.3 Electrocardiograms	Requirement for consistency in technicians for each participant updated to allow any appropriately trained personnel to perform the ECG	For logistical reasons	Non-substantial
Section 8.2.4 Clinical Safety Laboratory Assessments	Estimated glomerular filtration rate added to the	Additional laboratory safety assessment	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	list of laboratory safety variables in Table 6		
Section 9.4.2.1 Primary Endpoint	Site removed from statement of random effects. Clarified that 'visit' in the model specification only refers to the weekly visits during treatment. Clarified that subgroup analyses are additional (not primary) analyses.	Text modification to clarify evaluation of primary endpoint	Non-substantial

Amendment 3 (09 June 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The Clinical Study Protocol (CSP), Final 3.0, dated 10 March 2021, was updated to clarify study stop criteria, procedure for written Informed Consent in case of SARS-CoV-2 pandemic situation, study conduct mitigation during study disruptions due to COVID-19 pandemic, SAE reporting, time and reason for DSMB meetings, home nursing, and to update COVID-19 guidances. Numerous other minor editorial updates also made throughout.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3, Table 1	Deletion of cross-reference for blood sample collection for CCI [redacted]	To clarify that this cross-reference was previously added erroneously.	Non-substantial
Section 4.1.3, Section 4.1.4 Appendix G	Inclusion of references to applicable appendices	Clear reference for study conduct due to SARS-CoV-2 or similar pandemic has to be provided in addition to the general reference to cases of civil crisis, natural disaster, or public health crisis	Non-substantial
Section 4.4.1.	Change of wording to clarify that the study will be terminated prematurely in case specified stopping criteria are fulfilled.	To provide clear instructions/ stopping criteria	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.3.9	Change of wording to clarify the time requirements for SAEs reporting	To provide clear timeframes for the reporting of SAEs	Non-substantial
Section 9.6	Change of wording to clarify time and reason for DSMB meetings	To clarify when and how often the DSMB will meet	Non-substantial
Appendix F 2	Inclusion of clarifying text regarding home nursing visits	Text has to be clarified regarding local regulations for home nursing.	Non-substantial
Appendix F 5	Inclusion of updated EMA and BfArM guidance	Reference to updated guidances has to be provided	Non-substantial

Amendment 4 (13 Jan 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The Clinical Study Protocol (CSP) Final 4.0, dated 09 Jun 2021, was amended to reduce the sample size for Part 2b based on the expectation on effect size for the CCI mg dose and by utilizing the total number of placebo participants from both Part 2a and Part 2b to achieve satisfactory power, to modify the PK and ADA sampling timepoints for Part 1b and Part 2a and 2b, to add clarification that women who are breastfeeding or planning to become pregnant are excluded from study participation and to update to the definition of the covariate eosinophil count group.

A number of additional clarifications and minor editorial changes have also been added.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Overall Design, Number of Participants, Sample Size; Section 4.1.1; Figure 3, Section 4.1.2 Section 9.2	Total number of participants in Part 2 changed from 360 to 300 by reducing the number of participants in Part 2b/CCI mg dry powder inhaler CCI from 80 to 40 and in Part 2b/placebo from 40 to 20 and sample size considerations updated	Sample size for Part 2b was reduced based on the higher expectation on effect size for the CCI mg dose (targeting 200 mL instead of 175 mL) and by utilizing the total of 100 placebo participants (80 from Part 2a and 20 from Part 2b) to achieve satisfactory power	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Objective and Endpoints; Section 3, Table 4	Removal of reference to at-home monitoring for FEV_1	To clarify that home FEV_1 measurements form part of the e-Diary alert process, in-clinic spirometry assessment will be used to assess the study safety objective and will primarily be used for decision making	Non-substantial
Sections 1.1 Synopsis, General Statistical Consideration Section 4.1.2 Section 9.5	Main purpose of interim analysis changed to futility analysis	A futility analysis may be needed to inform internal AZ portfolio decisions	Non-substantial
Section 1.3 Table 1	Addition of '2 hour post' spirometry to clarify time point	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2	Addition of 'in-clinic' to FeNO test	Added for clarification as at-home assessments are also performed	Non-substantial
Section 1.3 Table 1 and Table 2, Section 5.1	Addition of language to clarify requirement for negative serum pregnancy test at Screening as per Schedule of Activities	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2, Section 5.2, Section 8.2.4, Table 6	Addition of text to allow for inclusion of participants with previous vaccination history for hepatitis B and positive anti-hepatitis B surface Ag at Screening can be included into the study following providing negative PCR test Addition of hepatis B PCR test to laboratory safety variables	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2, Section 5.1.3	Addition of language to clarify CRP testing requirements	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2	Addition of PK and ADA sampling timepoints	Addition of PK and ADA timepoints to further characterize the PK and ADA profile	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 Table 2, Section 4.1.2, Section 8.5.1.2	Number of participants for PK intense sampling arm updated to 'approximately 20 participants per treatment arm'	Wording corrected	Non-substantial
Section 1.3 Table 2	Addition of weeks in the Schedule of Activities	Added for clarification as endpoints are listed in weeks	Non-substantial
Section 1.3 Table 2, Section 8.6.2	CCI [redacted]	Updated as a result of logistics and feasibly of sampling	Non-substantial
Section 1.1 Synopsis, Intervention Groups and Duration Section 1.3 Table 2, Section 8.5.2	Increased window (Part 1) and removal (Part 2) of final ADA assessment	Given the short half-life of AZD1402 and experience with other non-monoclonal antibody therapeutic biologicals, measurements up to Day 56 is considered adequate for ADA characterisation	Non-substantial
Section 3 Table 3	Replaced 'Week 4' with 'Day 28', in the definition of exploratory endpoints in Part 1	Added for clarification as weeks are not referenced in Schedule of Activates for Part 1	Non-substantial
Section 5.2	Addition of the exclusion criterion: 'Women who are pregnant or breastfeeding, or who are planning to become pregnant during the study'	Additional clarification that women who are breastfeeding or planning to become pregnant are excluded from study participation	Substantial
Section 5.3.4	Update of time participants should abstain from donating blood and plasma from 5 half-lives to 28 days	Added for consistency with Informed Consent Form language	Non-substantial
Section 6.3 Section 9.4.4.1	References to plasma for PK samples replaced with 'serum'	Updated to remove erroneous inclusion previously	Non-substantial
Section 6.4	Definition for compliance added	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2, Section 7.1.1	Addition of Intervention Discontinuation visit and text to clarify steps to be taken when a participant withdraws from study intervention	Added for clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 7.1.2.1	Wording added to clarify FEV_1 in-clinic assessment will be used	Added for clarification	Non-substantial
Section 8.1.1	Wording added to clarify spirometry assessments should be performed pre-dose	Added for clarification	Non-substantial
Section 8.1.5 Section 8.3.5 Section 9.3, Table 7 Section 9.4.2.1 Section 9.4.3.1 Section 9.5	Minor text updates to align with the statistical analysis plan	Added for clarification	Non-substantial
Section 8.2.4 Section 9.4.1 Section 9.4.4	Vendor names replaced with generic wording	Administrative change to align with AZ standards	Non-substantial
Section 8.2.4, Table 6	Further information of cytokine assessments	Added for clarification	Non-substantial
Section 9.4.2.1	Update of definition of covariate eosinophil count group from '150 to 299, ≥ 300 cells/μL' to '< 300, ≥ 300 cells/μL'	To account for patients who may have eosinophil count lower than 150 cells/μL on Day 1	Substantial
Appendix A 5	Wording added to clarify when decision making is made by the SRC	Added for clarification	Non-substantial

Amendment 5 (04 Mar 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The Clinical Study Protocol (CSP) Final 5.0, dated 13 Jan 2022, was amended to redefine the stopping criteria and update the inclusion criteria for Part 2. The study stopping criteria have been adjusted to reflect the role of the Data Safety Monitoring Board (DSMB) in evaluating all clinical data, including spirometry, as applicable to the larger sample size and expected variability in the Part 2 participant population. Additionally, the individual suspension and stopping criteria have been amended to distinguish between criteria for Part 1 and Part 2 as applicable to different participant populations and variability in home assessment spirometry, in particular for Part 2 where there is no residential period. The inclusion criteria were updated to allow more flexibility in recruitment around ICS-LABA guidance and asthma exacerbations.

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1, Section 1.2 Figure 1, Section 1.3 Table 1	Extension to period of collection of additional ADA samples from 169 days ± 1 month to up to a year after randomisation.	To further characterise ADA profile and permit sampling following SRC unblinded data review	Non-substantial
Section 1.1 Overall Design Part 2, Section 4.1.2	Updated text to state Part 2b 3 dose levels 'may' run in parallel.	Clarification that the Part 2b decision to proceed is dependent on Part 1b completion with SRC review and may commence after the completion of Part 2a.	Non-substantial
Section 1.1, Section 9.5	Text added to interim analysis section to state it may be performed after Part 2a.	An efficacy evaluation of the primary endpoint may be performed to inform internal AZ portfolio decisions	Non-substantial
Section 1.3 Table 1 and Table 2, Section 8.1.4	Updates made to clarify subjects receive the e-Diary for completion at home from Visit 2, compliance checks will be done following this and e-diary completion is twice daily throughout study.	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2	Timing of ECG before administration of study intervention clarified to be "within" 75 min.	Added for clarification	Non-substantial
	Footnote added to clarify urinalysis samples taken pre-dose on Day 1	Added for clarification	Non-substantial
	Footnote added to clarify all urine pregnancy samples taken pre-dose.	Added for clarification	Non-substantial
Section 1.3 Table 2	Footnote added to baseline samples to confirm they are taken pre-dose.	Added for clarification	Non-substantial
Section 1.3 Table 1 and Table 2	Updated to clarify FeNO measurement is to be	Added for clarification	Non-substantial

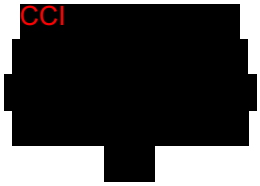
Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	performed in the morning and evening.		
Section 1.3 Table 2	Removal of text in footnote u that duplicated central laboratory assessment.	Removed for clarification	Non-substantial
Section 4.1.3	Bullet added to allow centralised assessments to be performed locally during study disruptions due to cases of civil crisis, natural disaster, or public health crisis.	Added for clarification	Non-substantial
Section 4.4.1, Section 7, Section 7.1.1, Section 7.1.2.1, Section 7.1.2.2, Section 8.1.5	Study stopping and suspension criteria redefined to distinguish between Part 1 and Part 2.	Study stopping criteria adjusted to reflect the role of the DSMB in evaluating all clinical data, including spirometry, as applicable to the larger sample size and expected variability in the Part 2 participant population. Individual suspension and stopping criteria amended to distinguish between criteria for Part 1 and Part 2 as applicable to different participant populations and variability in home assessment spirometry (no residential period in Part 2)	Substantial
Section 5.1	Updates added throughout criteria to clarify that reference to Visit 1 includes the Screening Period	Added for clarification	Non-substantial
Section 5.1.2, Section 6.5	Additional guidance on dose stability and ICS-LABA device in inclusion criteria 18.	Added for clarification	Substantial
Section 5.1.2	Inclusion criteria 20 amendment to extend the period of exacerbations from 12 months to	Amended to optimize selection of the participant population in view of the	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	3 years prior to Screening.	SARS-CoV-2 pandemic restrictions	
Section 6.1.3	Text updated to clarify participants in Part 2 receive training at Visit 3 only.	Updated for clarification	Non-substantial
Section 8.1.12	Clarification on the term 'severe exacerbation'.	Added for clarification	Non-substantial
Section 8.1.5, Section 8.3.5	Clarification on AESI definition to distinguish respiratory infections from non-respiratory, to clarify AESI reporting based on Investigators' assessment.	Added for clarification	Non-substantial

Amendment 6 (03 Aug 2022)

The Clinical Study Protocol (CSP) version 6.0, 04 Mar 2022 has been amended to optimize recruitment into the [redacted]mg dose arm which is expected to inform the primary endpoint. The CSP changes include the removal of the [redacted]mg dose and stopping the [redacted]mg dose arm in Part 2. The [redacted]mg dose level has been removed in Part 2 as data from earlier studies indicate that similar efficacy is expected at the [redacted] mg dose. The rationale to stop randomisation to the [redacted]mg dose arm in Part 2 is to optimize recruitment to reach the required number of evaluable participants for the primary endpoint comparison of efficacy between [redacted]mg and placebo. The [redacted]mg will be evaluated to inform the dose-response, safety profile and PK profile. The inclusion/exclusion criteria have been amended following the safety review committee outcome for Part 1 of the study, aligning with the intended target population of moderate to severe asthma patients and considering general medical treatment and practice. Furthermore, the Schedule of Activities has been modified to simplify the protocol, decrease the number of assessments and reduce patient and site burden.

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Section 1.3 Section 3 Section 4.1.2 Section 4.2	Change from baseline SGRQ score to Week 4 has been removed as secondary endpoint	SGRQ removed as ACQ-6 is considered sufficient to inform Patient Reported Outcome scores over the 4 week treatment period	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.1.10 Section 9.4.2 Appendix J References			
Section 1.1 Section 3			Non-substantial
Section 1.1 Section 4.1	Updated number of countries participating in the study	Updated recruitment planning	Non-substantial
Section 1.1 Section 4.1.2 Section 9.2	Updated section based on amended study design in Part 2: Total number of participants amended from 300 to approximately 180 by removing the [redacted] mg dose arm and stopping recruitment into the [redacted] mg dose arm	Phase 1 study data indicate similar efficacy is expected at the [redacted] mg dose, therefore evaluating the [redacted] mg dose is sufficient to inform the primary endpoint. Stopping the [redacted] mg dose arm will optimize recruitment to reach the required number of evaluable participants for the primary endpoint comparison of efficacy between [redacted] mg and placebo. The [redacted] mg will be evaluated to inform the dose-response, safety profile and PK profile.	Substantial
Section 1.1 Section 9.4.2.2 Table 4	Change from baseline in post-bronchodilator FEV_1 average over the 4-week Treatment period	Correction as post-bronchodilator spirometry is not performed during the treatment period	Non-substantial
Section 1.2	Updated schema consistent with study design update	Updated to reflect removal of [redacted] mg dose and adjusted recruitment into the [redacted] mg dose arm in Part 2	Non-Substantial
Section 1.3	Updated study drug inhalation training to be added at Visit 2 (run-in) for both Part 1 and Part 2	To correct inconsistencies in the protocol	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3	Mandatory SARS-CoV-2 PCR to be removed from screening visit	Amended to permit Investigators to perform SARS-CoV-2 PCR tests as per local guidelines and as clinically indicated	Non-substantial
Section 1.3	Part 2 Schedule of assessments updated to reflect updated endpoints, removal of CCI [redacted] timepoints, laboratory sampling and footnote amendments made in spirometry footnote k, ECG footnote m, PK measurements-footnote x and Proposed samples and time footnote aa	Assessments aligned with updated endpoints. Removal of blood sampling and/or assessments at run-in, Day 7 and Day 56 not required to inform primary or secondary endpoints. Reduction in overall number of procedures to reduce protocol complexity, site and patient burden.	Non-substantial
Section 1.3	Part 1 Schedule of Assessments updated	For clarification	Non-substantial
Section 1.3 Section 8.1.1	Clarification on post-randomisation spirometry assessment time window	For clarification	Non-substantial
Section 2.3.1.1	Further risk mitigation section updated	Section reworded and aligned with exclusion criteria update	Substantial
Section 4	Updated Figure 3 based on updated study design	To update study design and number of countries participating in the study	Non-Substantial
Section 4.1.2 Section 5.1.2 Section 5.1.4	Part 2 randomisation criterion updated FEV_1 range inclusion criteria to 50% to 85%. Amended throughout the protocol as applicable	Amended following positive outcome of Part 1a SRC and to align with intended target population	Substantial
Section 5	Updated text to clarify CRP retest at Visit 2 may be repeated during the run-in period	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.1	Updated on female and male contraception requirements after last study dose	Updated to reflect AZD1402 short half-life and time required for epididymal maturation and production of seminal fluid in an environment which is investigational drug free	Substantial
Section 5.1 Section 5.3.4	Removal of inclusion criterion that a participant's influenza/pneumonia vaccination should be up to date as per local guidelines, and added as a recommendation	To reflect real world treatment history of target population	Substantial
Section 5.1.2	Part 2 inclusion criterion updated to include historically documented evidence of asthma within the 5 years prior to Visit 1	Updated to permit historical evidence of an asthma diagnosis	Substantial
Section 5.1.2	Part 2 updated to include patients on medium-to-high dose ICS for at least 6 months prior to screening Amended throughout the protocol as applicable	Updated to include target population of uncontrolled moderate to severe asthma patients	Substantial
Section 5.2	Separation of exclusion criteria and time frame added on evidence of any active clinically important pulmonary disease, other than asthma, within 5 years at screening, and history of pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts	For clarification	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 5.2	Removal of exclusion criteria on participants with a positive diagnostic assess SARS-CoV-2 nucleic acid test (PCR), and further clarification of diagnosis of COVID-19	Amended to perform diagnostics as per local guidelines and as clinically indicated	Substantial
Section 5.2	Criteria for evidence of active or untreated latent TB infection (LTBI) updated	For clarification	Substantial
Section 5.2	Exclusion criteria related to current or history of malignancy updated	Adjusted as per product safety specification requirements	Substantial
Section 5.2	Removal of exclusion criteria of Pre-bronchodilator FEV_1 decrease or increase in Part 2	Removed as per protocol population include uncontrolled moderate to severe asthma patients	Substantial
Section 5.2	Exclusion criteria updated to permit inclusion of participants with a positive anti-hepatitis C antibody test and negative PCR test	For clarification	Substantial
Section 5.4	Clarification regarding re-screening in participants with positive SARS-CoV-2	Adjusted to permit re-screening within 2 weeks where infection has resolved	Non-substantial
Section 6.1.3	Included inhaler training at visit 2 for both Part 1 and Part 2 based on schedule of activities	To correct inconsistencies in the protocol	Non-substantial
	Updated to add flexibility to prolong run-in at Sponsor's discretion, in the event of technical problems and e-diary cannot be completed	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.5.2	Updated text to align with revised inclusion criteria	For clarification	Non-substantial
Section 6.5.2	Updated medium dose ICS for Part 1 and medium-to-high dose ICS for Part 2	Updated to align with updated inclusion criteria	Substantial
Section 8.1.2	Updated text to align with inclusion criterium; medication withhold periods before reversibility testing added	For clarification	Non-substantial
Section 8.1.3 Section 4.1.2	Home FeNO assessment removed in Part 2. Clarification that Home FeNO measurements will only be performed in Part 1	Safety and Secondary FeNO endpoints will be informed by in-clinic assessments	Non-substantial
Section 1.1 Section 1.3 Section 3 Section 4.1.2 Section 4.2 Section 8.1.10 Section 9.4.2 Appendix H2 Appendix J References	Change from baseline SGRQ score to Week 4 has been removed as secondary endpoint	SGRQ removed as ACQ-6 considered sufficient to inform Patient Reported Outcome scores over the 4 week treatment period	Non-substantial
Section 1.1 Section 1.3 Section 3 Section 4.1.2 Section 8.1.10 Appendix H2 Appendix J References	CCI [redacted]	Exploratory endpoint removed to reduce patient burden	Non-substantial
Section 1.1 Section 1.3 Section 3 Section 4.1.2 Section 8.1.4	CCI [redacted]	Exploratory endpoint removed to reduce patient burden	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.1.10 Appendix H5 Appendix J References			
Section 1.1 Section 1.3 Section 3 Section 4.1.2 Section 8.1.10 References	Change from baseline Cough VAS over the treatment period has been removed as an exploratory endpoint in Part 2 Clarification that Cough VAS will only be performed in Part 1	Exploratory endpoint removed to reduce patient burden	Non-substantial
Section 9.4.4.1	Update on PK parameters Addition of Dose normalised AUClast	To update on PK parameters derivations	Non-substantial
Section 9.4.3 Section 9.4.3.1	SAS to be replaced by SS	For clarification	Non-substantial
Section 9.5	Removed option to perform interim analysis after Part 2a and removed reference to Part 2b	Updated based on removal of Part 2b	Non-substantial
Section 9.6 Appendix A5.2	Updated SRC data review description in line with removal of Part 2b	For clarification	Non-substantial

11 REFERENCES

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

GINA 2022
Available at https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf (accessed 02 Aug 2022)

Greening, et al, 1994
Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994;344:219–224.

Hopkins, et al 2009
Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin. Oto. 2009;34:447–454.

Jones, et al. 1991
Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Resp. Med. 1991; 85: 25-31.

Juniper, et al. 1999
Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999 Oct;14(4):902-907.

Juniper, et al. 2006
Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Resp. Med. 2006 Apr; 100 (4):616-621.

Miller, et al. 2005
Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

Ray, et al. 2016
Ray A, Raundhal M, Oriss TB, Ray P, Wenzel SE. Current concepts of severe asthma. J. Clin. Invest. 2016;126:2394–2403.

Reddel, et al. 2009
Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and

exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59–99.

Rothe and Skerra, 2018
Rothe C, Skerra A. Anticalin® proteins as therapeutic agents in human diseases. BioDrugs 2018;32(3):233-43.

Woolcock, et al. 1996
Woolcock A, Lundback B, Ringdal N, and Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit. Care Med 1996;153:1481–88.

World Allergy Organisation 2013
WAO White Book on Allergy | World Allergy Organization (World Allergy Organization). Available from: URL: http://www.worldallergy.org/UserFiles/file/WhiteBook2-2013-v8.pdf

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