Clinical Study Protocol	
Study Intervention	Mitiperstat (AZD4831)
Study Code	D6582C00001
Version	5.0
Date	07 December 2023

A Phase IIa Randomised, Double Blind, Placebo Controlled, Parallel Arm, Multi-Centre Study to Evaluate the Efficacy and Safety of Mitiperstat (AZD4831), for 12-24 Weeks, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s):

Registry	**ID**
EudraCT	2022-002441-18
IND	161799

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

Version Scope: Global

Brief Title: An Efficacy and Safety Study of Mitiperstat (AZD4831) (MPO Inhibitor) vs Placebo in the Treatment of Moderate to Severe COPD

Redacted for Public Disclosure

Study Phase: Phase IIa

Acronym: CRESCENDO

Study Physician Name and Contact Information will be provided separately.

The Study Physician is responsible for the clinical integrity of the study.

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SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 5.0	07 December 2023
Version 4.0	28 April 2023
Version 3.0	13 January 2023
Version 2.0	30 June 2022
Original Protocol	05 May 2022

CSP Version 5.0, 07 December 2023

This modification 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 and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

The primary rationale for the modifications in this CSP is to increase the sample size, due to changes in statistical assumptions, to ensure that the study is adequately powered to assess the primary and key secondary endpoints.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall Design, Section 9.2 Sample Size Determination	The estimated study sample size was changed from approximately 480 to 677 screened participants. The estimated number of participants randomised/assigned to the study intervention was changed from approximately 288 to 406. The estimated number of evaluable participants was updated from approximately 288 to 406 (from 144 to 203 in each arm).	Due to changes in statistical assumptions, the sample size was modified to ensure adequate power to assess the primary and key secondary endpoints.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 9.2 Sample Size Determination	The statistical assumptions were revised based on available data. The text was amended as follows: "A total of ~~113~~ **194** first COPDCompEx events (estimated to require ~~144~~ **203** participants per arm) will provide 80% power ~~to detect a 30% decrease between the 2 arms~~ at the two-sided 10% level of statistical significance **to detect a hazard ratio of 0.7 in the mitiperstat (AZD3851) 5 mg QD arm based on a 24-week**~~. A 12-week~~ first COPDCompEx event ~~rate~~ **risk of 55% assumed** in **the** placebo arm ~~of 48%,~~ **(**constant over the course of the study**).** ~~was assumed.~~	Available blinded study data was used to update statistical assumptions and study sample size to ensure adequate power to assess the primary and key secondary endpoints.
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall Design, Section 4.2 Scientific Rationale for Study Design, Section 7.1.4 Participant Discontinuation at Study End, Section 9.2 Sample Size Determination Section 9.4.2.1 Primary Endpoint	Enrolment will be stopped after at least "**194"** rather than 113 first COPDCompEx events have occurred.	Due to the changes in statistical assumptions and increase in sample size, the number of first COPDCompEx events required before stopping enrolment was increased to ensure adequate power to assess the primary and key secondary endpoints.

Section Number and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria, Section 8.2.7 Optional Computer Tomography Scan	Exclusion criterion 7 and 7 (g) were amended as follows: 7: "Any other clinically relevant abnormal findings on physical examination, laboratory testing including haematology, coagulation, serum chemistry, or urinalysis; or ~~chest CT scan at screening or~~ **recent lung imaging prior to** randomisation, which in the opinion of the investigator or medical monitor may compromise the safety of the participant in the study or interfere with evaluation of the study intervention or reduce the participant's ability to participate in the study. In addition, if a participant meets any of the criteria below, they will be excluded from the study:..." 7(g): **"Recent lung imaging that requires immediate diagnostic investigation or follow-up. If initial repeat surveillance imaging has been undertaken, and the abnormality is considered low risk of malignancy, the participant may be eligible for enrolment following confirmation with the AstraZeneca medical monitor.**~~Chest CT scan findings requiring further investigation or repeat CT surveillance scan before SV8.~~" Additional wording was added in Section 8.2.7 to reflect the change to the exclusion criteria.	To ensure that appropriate investigation of any suspicious lesion observed on any previous lung imaging modality is undertaken prior to potential enrolment.
Section 5.2, Exclusion Criteria	Exclusion criterion 7(f) was amended: "In addition, if a participant meets any of the criteria below, they will be excluded from the study:…" "Any clinically significant rhythm, conduction, or morphology abnormalities in the 12-lead ECG including but not limited to corrected QT interval (Fridericia) (Vandenberk et al 2016) > 450 ms. **Participants with atrial fibrillation or flutter and optimally controlled ventricular rate at resting < 100 beats per minute might be included as judged "by the investigator** ~~Atrial fibrillation is exclusionary."~~	To allow participants with stable atrial fibrillation or atrial flutter to be included in the study. This is supported by lack of specific cardiac safety signal in previous preclinical and clinical studies.
Section 5.2, Exclusion Criteria	Exclusion criterion 10 was amended: "Use of domiciliary non-invasive positive pressure ventilation device, including BiPAP~~ and CPAP~~. **CPAP for the purpose of treating obstructive sleep apnoea is allowed**."	To determine that the use of BiPAP is excluded and reflect the change that the use of CPAP is acceptable.

Section Number and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria	Exclusion criterion 12 was amended: "~~History or ongoing allergy/hypersensitivity reactions to drugs (including but not limited to rash angioedema, acute urticaria)~~ **Active drug-induced hypersensitivity skin reaction or history of SCARS (including DRESS, SJS/TEN, and AGEP)**."	To clarify the details of the exclusion criteria for hypersensitivity skin reactions and severe cutaneous adverse reactions.

Bold signifies added text, strike through signifies deleted text.

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Throughout.	Minor changes were made to formatting and wording throughout the document for example to fix errors and improve grammar and sentence/section structure without change of meaning.	To improve clarity and readability.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Change to the text for the safety estimand related to strategy for intercurrent events. "Primary: while on treatment – if an intercurrent event occurs ~~after the safety follow up~~, any subsequent safety data will not be taken into consideration in the safety evaluation."	To amend an error in the previous version of the CSP. The text does not correspond to the estimand while on treatment.
Section 1.1 Synopsis, Section 4.1 Overall Design,Section 9.5 Interim Analysis, Section 9.6 Data Review Committee, Appendix A 5 Committees Structure	Sections of text relating to the roles of the URC and DRC were updated as follows: "The DRC will assess safety and will have access to ~~interim~~IA outcome data~~, if required~~ **(including all adverse event data)**." "The ~~DRC~~ **URC** will ~~perform~~ **review efficacy data** from the IA and **the DRC will** perform periodic safety monitoring with a focus on skin reactions and pneumonia. See Appendix A 5 for details." Text removed from Section 9.6 due to repetition: ~~A URC will be embedded in the study to carry out the IA. For details on the URC for this study, see Appendix A 5.~~ "~~The~~ **At the time of the IA, the** DRC will assess the safety **profile (ie, all AE data) of mitiperstat (AZD4831)** and will have access to **IA** ~~interim analysis~~ outcome data, if required. ~~This evaluation will be performed at the same time as the IA.~~ Additional details will be contained in the DRC Charter."	To clarify the roles of the DRC and URC and to clarify the extra data the DRC will evaluate at the time of the IA.
Section 1.1 Synopsis, Section 9.5 Interim Analysis	Text related to the administrative IA conducted by the URC was amended as follows: "An administrative IA will be conducted by the URC after ~~45~~ **136** (~~40%~~ **70%** of the required ~~113~~ **194**) first COPDCompEx events have occurred." Text in the Synopsis was further amended: "It will allow an early assessment of efficacy for mitiperstat (AZD4831) **used for further development of this drug programme**..."	To update the sample size and percentage of COPDCompEx events required for the administrative IA to be conducted due to study progression and change in overall sample size and to clarify that the unblinded IA results will not be used to inform decisions for the ongoing study.

Section Number and Name	Description of Change	Brief Rationale
Section 1.2 Schema, Section 1.3 Schedule of Activities	The visit day/week window description for SV8 in the SoA was amended to +14 days or +2 weeks **post-SV7/EDV** rather than +14 days or +2 weeks post-treatment.	To amend an error in the previous version of the CSP.
Section 1.3 Schedule of Activities	Change in formatting to show the Q-SAW substudy informed consent time between SV1 and SV5. Addition of note: **Consent can be obtained any time up until SV5.**	To clarify that consent for Q-SAW substudy can be obtained any time from SV1 to SV5. No change to the study procedure.
Section 1.3 Schedule of Activities	Change in formatting to show the Patient Experience Interview substudy informed consent time between SV1 and SV7. Addition of note: **Consent can be obtained any time up until SV7.**	To clarify that consent for the Patient Experience Interview substudy can be obtained any time from SV1 to SV7. No change to the study procedure.
Section 1.3 Schedule of Activities, Section 5.2 Exclusion Criteria, Section 5.4 Screen Failures, Section 8.2.7 Optional Computer Tomography Scan	Changes to wording to reflect that the CT scan assessment is important but optional.	To change and clarify the details for the CT scan assessment.
Section 1.3 Schedule of Activities, Section 8.3.4 Clinical Safety Laboratory Tests, Section 8.4.9 Adverse Events of Special Interest	Removed mandatory ANCA assessment during the study and clarified that ANCA sample is optional at the discretion of the investigator.	This assessment is no longer mandatory given the low prevalence of history of ANCA positive vasculitis or skin disease. Optional ANCA assessment is still available if needed.
Section 1.3 Schedule of Activities, Section 8.8.2 Mandatory Genetic Analysis Sample Collection, Appendix B 5 Guide to Skin Reaction Assessment	The mandatory genetic analysis sample collection was removed from the schedule of activities and the subsection detailing the assessment was deleted. Subsequent Section 8.8.3, Optional Cell-free DNA Analysis Sample Collection was renumbered as Section 8.8.2.	To determine that no mandatory genetic samples are required in the study.

Section Number and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Inclusion criterion 5 was amended to ≤ 100 cells/µL rather than ≤ 100 cells/mL	To amend an error in the previous version of the CSP.
Section 5.2 Exclusion Criteria	Exclusion criterion 19 was amended to "including but not limited to TSH ≥ **10 mIU/L**" rather than ≥ 10 mIU/mL.	To amend an error in the previous version of the CSP.
Section 6.1.1 Medical Devices Including Combination Products with a Device Constituent	The following text was added: **ArtiQ.QC will be integrated into ZEPHYRx application for an instant artificial intelligence–based over-reading of spirometry against ATS/ERS 2019 standards. Meanwhile ArtiQ.RBM software will also be utilised in ZEPHYRx and UNIFY, for risk-based quality management analysis of spirometry and identification of sites that may require quality improvement initiatives.** **Both ArtiQ.QC and ArtiQ.RBM are not considered to meet the definition of a medical device as it only performs quality control and quality management functions. It will not be used as the basis for any clinical decision making or patient treatment.**	To provide details of ArtiQ as a vendor for quality control assessment and ensure patient-level data can be transferred to ArtiQ for risk-based quality management purposes.
Section 6.9.1 Rescue Medicine	The text was amended as follows: "The following ~~rescue medications~~ **SABAs, as per local SoC,** may be used **during the study as rescue medication...**"	To clarify that SABA medication could be used as per local SoC.
Section 9.3 Populations for Analyses	Full analysis set population description amended: "Will include all randomised participants who received at least 1 dose of study intervention ~~and have post-baseline data for COPDCompEx~~. Participants will be analysed according to planned treatment. Efficacy analyses will be based on the FAS.	To correct an error from the previous version of the CSP. Post-baseline data for COPDCompEx is not required for inclusion in the full analysis set.

Bold signifies added text, strike through signifies deleted text.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACM	Ambulatory cough monitor
ADL	Activities of Daily Living
AE	Adverse event
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AESI	Adverse event of special interest
AGEP	Acute generalised exanthematous pustulosis
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
ANCA	Anti-neutrophil cytoplasm antibodies
ATS/ERS	American Thoracic Society/European Respiratory Society
AST	Aspartate aminotransferase/transaminase
AWE	Acute worsening event
BCSS	Breathlessness, Cough, and Sputum Scale
BD	Bronchodilator
BDRM	Blinded data review meeting
BiPAP	Bilevel Positive Airway Pressure
BP	Blood pressure
BSA	Body surface area
CAT	Chronic obstructive pulmonary disease Assessment Test
CFR	Code of Federal Regulations
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
COPDCompEx	COPD Composite Exacerbations (composite measure of chronic obstructive pulmonary disease)
COVID-19	Coronavirus 2019
CPAP	Continuous positive airway pressure
CRO	Contract research organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DILI	Drug Induced Liver Injury

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DRC	Data Review Committee
DRESS	Drug reaction with eosinophilia and systemic symptoms
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
e-Diary	Electronic diary
EDV	Early discontinuation visit
EMA	European Medicines Agency
EU	European Union
EXACT	The Exacerbations of Chronic Pulmonary Disease Tool
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Obstructive Lung Disease
GPRI	General Practitioners Research Institute
HbA1c	Glycated haemoglobin
HCP	Healthcare professional
HfpEF	Heart failure with preserved ejection fraction
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
hsCRP	High sensitivity C-reactive protein
IA	Interim analysis
IATA	International Airline Transportation Association
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long-acting beta-adrenoceptor agonist

Abbreviation or special term	Explanation
LAMA	Long-acting muscarinic antagonist
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MPO	Myeloperoxidase
mRNA	Messenger ribonucleic acid
NIMP	Non Investigational Medicinal Product
NT-proBNP	N-terminal pro B-type natriuretic peptide
OCS	Oral corticosteroids
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PEF	Peak expiratory flow
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per Protocol Set
PRO	Patient reported outcome
QD	Once daily
Q-SAW	Qualitative Study into Acute Worsening Events
RTSM	Randomisation and Trial Supply Management
SABA	Short-acting beta agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCARS	Severe cutaneous adverse reactions
SD	Standard deviation
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
SoC	Standard of care
SPFQ	Study Participant Feedback Questionnaire
SV	Study Visit
TB	Tuberculosis
TBL	Total bilirubin
TEN	Toxic epidermal necrolysis
t_{max}	Time to reach maximum concentration

Abbreviation or special term	Explanation
TPV	Third-party vendor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
URC	Unblinded Review Committee
USA	United States of America
VAS	Visual Analogue Scale

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase IIa Randomised, Double Blind, Placebo Controlled, Parallel Arm, Multi-Centre Study to Evaluate the Efficacy and Safety of Mitiperstat (AZD4831), for 12-24 Weeks, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

Brief Title: An Efficacy and Safety Study of Mitiperstat (AZD4831) (MPO Inhibitor) vs Placebo in the Treatment of Moderate to Severe COPD

Regulatory Agency Identifier Number(s):

Registry	ID
EudraCT	2022-002441-18
IND	161799

Rationale: This study will evaluate the efficacy and safety of the myeloperoxidase (MPO) inhibitor, mitiperstat (AZD4831) in the treatment of moderate to severe COPD. Patients with COPD represent a huge unmet medical need: COPD exacerbations are associated with accelerated decline in lung function, high mortality, worsening quality of life and comorbidities, and high healthcare costs. In addition, COPD is also frequently associated with other metabolic or cardiovascular comorbidities, which also contribute to impaired quality of life and poorer survival. Furthermore, current COPD therapies, which include combinations of inhaled long-acting beta-adrenoceptor agonist (LABA), long-acting muscarinic agonist (LAMA), and inhaled corticosteroids (ICS), and add-on anti-inflammatory agents, do not eliminate symptoms, disability, exacerbations, or the hospitalisations that are associated with COPD, and do not significantly alter the course of COPD.

There is evidence implicating MPO activity in promoting lung inflammation and injury in animals exposed to cigarette smoke, and high concentrations of (activated) MPO are associated with the progression of COPD in humans. Therefore, this study and the clinical development program for mitiperstat (AZD4831) will evaluate whether treating patients with COPD with mitiperstat (AZD4831) reduces exacerbations, and improves symptoms, quality of life, lung function, and other clinically-relevant outcomes including comorbidities in patients with COPD.

Objectives and Endpoints

Objectives	Estimand Description[a]
Primary	
To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPDCompEx event in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arm. **Endpoint:** time to first COPDCompEx event. **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** Primary estimand: while on treatment – if an intercurrent event occurs before first COPDCompEx event, the participant will be censored at the time of intercurrent event. Supportive estimand: treatment policy (reflects ITT principle) – after intercurrent event participants remain in the study so that the endpoint can be observed. Treatment policy strategy used to estimate the efficacy of mitiperstat (AZD4831) in 'real-world' conditions.
Secondary	
To assess the PK of mitiperstat (AZD4831) in patients with moderate to severe COPD.	**Population:** all participants who had received at least one dose of mitiperstat (AZD4831), and who had at least one measurable PK sample post dose. **Endpoint:** plasma mitiperstat (AZD4831) concentration-time profiles during the intervention and follow-up periods, and PK parameters. **Population level-summary measure:** summary statistics. **Strategy for intercurrent events:** while on treatment.
To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first moderate or severe COPD exacerbation.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** time to first COPD exacerbation event[b] **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** while on

Objectives	Estimand Description[a]
	treatment.
To assess the effects of mitiperstat (AZD4831) as compared to placebo on post-BD FEV1 in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in post-BD FEV1 after 12 weeks. **Population level-summary measure:** the difference in mean. **Primary estimand:** while on treatment. **Supportive estimand:** treatment policy.
To assess the effect of mitiperstat (AZD4831) compared with placebo on respiratory symptoms in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in EXACT, BCSS score, and Cough VAS at Week 12 and Week 24 **Population level-summary measure:** the difference in mean. **Strategy for intercurrent events:** while on treatment.
To assess the effect of mitiperstat (AZD4831) compared with placebo on disease impact in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in Total CAT measured in clinic at Week 12. **Population level-summary measure:** The difference in mean. Proportion of participants with change from baseline of -2 or less. **Strategy for intercurrent events:** while on treatment.

Objectives	Estimand Description[a]
Safety	
To assess the safety and tolerability of mitiperstat (AZD4831) compared with placebo in patients with moderate to severe COPD.	**Population:** all participants who received at least 1 dose of study intervention (Safety Analysis Set). **Endpoint:** safety and tolerability evaluations using AEs, SAEs, AESIs (skin reactions, including maculopapular rash, and infections, including pneumonia), vital sign measures, clinical laboratory assessments (clinical chemistry, haematology, and urinalysis), and ECG. **Population level-summary measure:** descriptive statistics eg, absolute counts and frequencies. **Strategy for intercurrent events:** Primary: while on treatment – if an intercurrent event occurs, any subsequent safety data will not be taken into consideration in the safety evaluation. Supportive: treatment policy – if an intercurrent event occurs, participants remain in the study and any safety data until Week 12 + safety follow-up will be taken into consideration in the safety evaluation.

[a] An estimand is a precise description of the treatment effect reflecting the clinical question posed by the study objective. It summarises at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Definition from FDA E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

[b] COPD Exacerbation: a worsening in the participant's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), may warrant a change in regular medication, and leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.
- Use of antibiotics to treat COPD exacerbation for at least 3 days.
- An inpatient hospitalisation due to COPD (defined as an inpatient admission ≥ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).
- Admission in emergency department or emergency room due to COPD for < 24 hours requiring intensive treatment.
- An episode of pneumonia.
- Results in death.

Moderate and severe COPD exacerbations are defined in Section 8.2.2.2.
Intercurrent events are events occurring after treatment initiation (eg, discontinuation of treatment, switching treatment, terminal events such as death) that affect either the measurement or interpretation of the summary measure (eg, hazard ratio) associated with the clinical question of interest.
This study contains 2 intercurrent events:

1 Treatment discontinuation (with the following reasons: SAE, death not due to exacerbation, COVID-19, pneumonia, other).
2 Prohibited medication.

AE = adverse event; AESI = adverse event of special interest; BCSS = Breathlessness, cough and sputum scale; BD = bronchodilator; CAT = COPD assessment test; COPD = chronic obstructive pulmonary disease; COPDCompEx = COPD Composite Exacerbations; ECG = electrocardiogram; EXACT = The Exacerbation of Chronic Pulmonary Disease Tool; FEV1 = forced expiratory volume in 1 second; ITT = intent-to-treat; PK = pharmacokinetic; SAE = serious adverse event; VAS = visual analogue scale.

For Tertiary/Exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design Synopsis:

A schematic is provided in Section 1.2 showing the overall study design.

This is a Phase IIa, randomised, placebo-controlled, double-blind, parallel-arm, event-driven study with an up to 24-week treatment time. It will be performed in approximately 100 sites across approximately 14 countries.

- Participants aged 40 to 80 years inclusive, with confirmed moderate to severe symptomatic COPD (forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] < 0.7, ≥ 10 pack-years smoking history, and post-BD FEV1 ≥ 25% predicted) who are at high risk of exacerbations despite being maintained on optimised standard of care (SoC) inhaled therapies (triple inhaled therapy [ICS + LABA + LAMA] or ICS + LABA dual therapy or LABA + LAMA dual therapy for participants who are deemed unsuitable for ICS) will be enrolled. Being at high risk of exacerbations is defined as participants fulfilling one or more of the following criteria:
  - ≥ 1 moderate or severe exacerbation in the last 2 years (defined as requiring systemic corticosteroids and/or antibiotics for at least 3 days' duration [or 1 injection of depot formulation], or hospitalisation for reason of acute exacerbation of COPD (AECOPD) in the 24 months prior to screening).
  - Frequent productive cough defined as positive answers to both of the following 2 questions:[1]
    - Over the past 3 months, I have coughed at least several days a week
    - Over the past 3 months, I have brought up phlegm (sputum) at least several days a week
  - Post-BD FEV1 of < 50% predicted

[1] Used with the permission of the St. George's Respiratory Questionnaire Steering Committee

- The study will explore an alternative community-based patient recruitment in some countries, utilising a network of Primary Care and Community COPD/Pulmonary Rehabilitation facilities to boost enrolment. The target countries with established Community COPD Clinic/Pulmonary Rehabilitation infrastructure will serve as participant recruitment centres or new sites.
- To reduce the burden on participants, Visits SV2, SV4, SV7/EDV, and SV8 will have a limited number of assessments and shortened duration, and Visit SV6 will be a "virtual visit" which will be performed away from the study site. This will be conducted over a telemedicine video conferencing facility based on technology provided by Zoom Inc (San Jose, California, USA), through the UNIFY platform, using a provisioned handheld device.

Cough Monitoring Substudy

A cough monitoring substudy will be performed alongside this study. In the cough substudy, a subset of participants (up to approximately 50 participants from each arm) from selected sites will be included. Twenty-four-hour cough frequency monitoring will be conducted at start of treatment (Visit SV3) and after 12 weeks of treatment (Visit SV5) using the VitaloJAK® Cough Monitor device. The substudy will also investigate whether average cough frequency is associated with lung function (eg, peak expiratory flow [PEF] or FEV1), cough/COPD symptom scores (eg, Breathlessness, Cough and Sputum Scale [BCSS], COPD Assessment Test [CAT] and Cough Visual Analogue Scale [VAS]) and sputum/blood biomarkers (eg, MPO concentration, neutrophil activation markers).

Q-SAW Substudy

The Q-SAW substudy will be performed alongside this study. In the Q-SAW substudy, a subset of approximately 40 participants from selected sites in selected countries will be included. Two remote, qualitative, semi-structured interviews will be conducted up to 6 weeks apart to provide a deeper understanding of day-to-day variations in symptoms and the impact of AWEs on the patient's life.

SPFQ Substudy

The SPFQ substudy will be performed alongside this study. Participants from selected sites in selected countries will have the option to provide feedback on their clinical study experience. Participants will complete the SPFQ in electronic format on the UNIFY platform at SV3, SV5, and SV7/EDV, using a provisioned handheld device. The aim of the substudy is to gain an understanding of patient experience in clinical studies and identify where improvements can be made in the clinical study process.

Patient Experience Interview Substudy

The patient experience interview substudy will be performed alongside this study and the data

from this qualitative substudy will complement the data from the quantitative SPFQ. In the patient experience interview substudy approximately 20 participants in total, from selected sites in selected countries, will be invited to attend a remote, semi-structured interview. The aims of the substudy are to understand how participant experience can be improved and to gain further insight into the participant perceptions and experiences of the digital technology used, including the virtual spirometry.

Brief Summary:

The purpose of this study is to measure benefit and safety of orally administered mitiperstat (AZD4831) as compared to orally administered placebo in participants with COPD. It is hypothesised that mitiperstat (AZD4831) will reduce airway inflammation and tissue damage, which could potentially lead to an improvement in lung function and/or reduce rate of decline in lung function.

Study details include:

- The study duration will be up to 30 weeks.
- The treatment duration will be up to 24 weeks.

Disclosure Statement: This is a parallel -group treatment study with 2 arms that is participant, investigator, and sponsor blinded.

- Number of Participants: Approximately 677 participants will be screened to achieve 406 randomised/assigned to study intervention and 406 evaluable participants.
- Participants will be randomised 1:1 to mitiperstat (AZD4831) 5 mg QD or placebo QD.
- Randomisation will be stratified by country.
- Enrolment will be stopped after at least 194 first COPDCompEx events have occurred. At this point, all participants enrolled in the study that have not yet completed SV5 should continue in the study to complete 12 weeks of treatment. For these participants SV5 and SV7/EDV should be combined into one visit. Participants who have already completed 12 weeks of treatment when study enrolment is stopped should attend SV7/EDV as soon as possible, continuing treatment until they do. All participants should attend SV8 14 ± 3 days after SV7/EDV.

Screened	Estimated 677 participants, assuming a screen failure rate of 40%
Randomised/assigned	Estimated 406 participants
Evaluable participants	Estimated 406 participants

Note: "Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomised/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Study Arms and Duration:

The entire study period is planned to take between 18 and 30 weeks for each individual participant: a 4-week screening period, minimum 12 weeks to a maximum 24 weeks of dosing, and 2 weeks of follow-up. The participant will be randomised into either mitiperstat (AZD4831) 5 mg or placebo treatment in the form of an oral tablet, taken once daily.

Data Monitoring/Other Committees: Yes

- **Unblinded Review Committee** A URC will be set up to perform an administrative IA on the primary efficacy endpoint (time to first COPDCompEx event).
- **Data Review Committee** A DRC will be set up to conduct periodic safety monitoring, with a focus on skin reactions and pneumonia. The DRC will assess safety and will have access to IA outcome data (including all adverse event data).

Statistical Methods

- The study is powered using COPDCompEx, a composite endpoint used to predict treatment effect on moderate and severe exacerbations of COPD. COPDCompEx captures clinically relevant deteriorations (diary events [eg, PEF], reliever use, symptoms, exacerbation events, and study dropouts resulting from a lack of efficacy) that fulfil specific criteria in terms of changes from baseline and deterioration over 5 days, combined with exacerbations, and 3-month COPDCompEx treatment effects have been shown to reflect treatment effects on exacerbations at 6 to 12 months.
- A total of 194 first COPDCompEx events (estimated to require 203 participants per arm) will provide 80% power at the two-sided 10% level of statistical significance to detect a hazard ratio of 0.70 in the mitiperstat (AZD4831) 5 mg QD arm based on a 24-week first COPDCompEx event risk of 55% assumed in the placebo arm (constant over the course of the study).

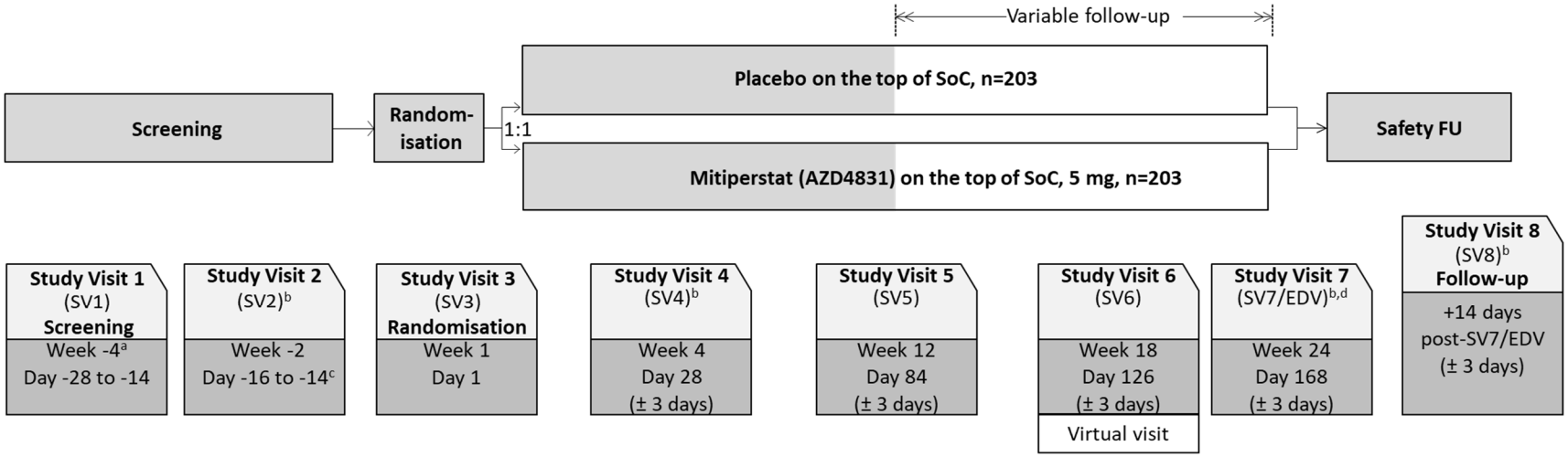
- The primary objective is to evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPDCompEx event in participants with moderate to severe COPD. The primary endpoint will be time to first COPDCompEx event. A logrank test and Cox's proportional hazards model will be used to analyse the time to first COPDCompEx event data.

A similar approach to that described for the primary efficacy endpoint will be applied to the secondary endpoint: time to first exacerbation.

- Other secondary assessments of efficacy include: time to first COPD exacerbation event, post-BD FEV1 at Week 12 compared to Week 1, MPO level and activity in sputum at Week 12 compared to baseline, and symptom scores.
- Plasma concentrations will be summarised by timepoint in all participants. Pharmacokinetic (PK) data for those participants with additional PK sampling at Visit SV5 will be used to derive plasma PK parameters such as maximum concentration (C_{max}) and time to reach maximum concentration (t_{max}).
- An administrative IA will be conducted by the URC after 136 (70% of the required 194) first COPDCompEx events have occurred. It will allow an early assessment of efficacy for mitiperstat (AZD4831) used for further development of this drug programme, based on the predictive probability of success, according to the decision framework and safety. No formal statistical test will be conducted, and no alpha will be spent at the IA.

1.2 Schema

Figure 1 Study Design



[a] SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure. Informed consent can be taken prior to SV1.
[b] To reduce the burden on participants, Visits SV2, SV4, SV7/EDV, and SV8 will have a limited number of assessments and shortened duration.
[c] Visit SV2 should occur 14 to 16 days before SV3 (Day 1).
[d] Participants discontinuing study intervention before SV7 should attend site for SV7 assessments as soon as possible as an EDV, then attend for SV8 assessments 14 (± 3) days later.

Enrolment will be stopped after at least 194 first COPDCompEx events have occurred. At this point, all participants enrolled in the study that have not yet completed SV5 should continue in the study to complete 12 weeks of treatment. For these participants SV5 and SV7 should be combined into one visit. Participants who have already completed 12 weeks of treatment when study enrolment is stopped should attend SV7 as soon as possible, continuing treatment until they do. All participants should attend SV8 14 ± 3 days after SV7/EDV.
EDV = early discontinuation visit; FU = follow-up; SoC = standard of care; SV = Study Visit.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Written informed consent/assignment of E-code	X								Informed consent can be taken prior to SV1.	Appendix A 3
Written informed consent for future use and/or genetic	X									Appendix D
Written informed consent for Cough substudy	X								Required only for participants of the cough substudy.	
Written informed consent for the Q-SAW substudy	←			X				→	Required only for participants of the Q-SAW substudy at selected sites. Consent can be obtained any time up until SV5.	Appendix L

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Informed consent for SPFQ substudy			X		X		X		Required only for participants of the SPFQ substudy at selected sites. Informed consent given within the UNIFY platform, using a provisioned handheld device.	Appendix M
Written Informed consent for the Patient Experience Interview substudy	←			X			→		Required only for participants of the Patient Experience Interview substudy at selected sites. Consent can be obtained any time up until SV7.	Appendix N
Verify eligibility criteria	X	X	X							5
Randomisation			X							6.3

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Optional high-resolution CT scan	←	X	→						The optional high-resolution CT scan could be performed as soon as main eligibility criteria are confirmed at SV1 which include blood test results, up to randomisation. If a CT scan is performed during the study, the local CT scan report must be obtained before randomisation.	8.2.7
Demography	X									
Medical and COPD history	X									
Assessment of COPD exacerbations	X		X	X	X	X	X			8.2.2
Smoking history	X						X		Includes e-cigarettes	

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Physical examination	X		X		X		X		Brief physical examination, except at SV3 (Day 1) and discontinuation visit, where a full physical examination is required. Additional assessments may be performed as clinically indicated.	8.3.1
Weight, height	X						X			
ECG	X		X		X					8.3.3
Vital signs	X		X	X	X		X	X		8.3.2
Lying and standing (orthostatic) BP test			X		X				Assessed at SV3 and SV5 prior to any required blood draw or study intervention. Also to be assessed 1 to 2 hours post dose at SV3. Orthostatic BP will be measured 1 and 3 minutes after the participant stands.	8.3.2

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Collection of AEs/SAEs	X	X	X	X	X	X	X	X	Participants should be reminded at each visit to contact the investigator immediately, if rash or skin reaction has developed. Non-Serious AEs will be collected from the first dose of study intervention onwards (see Section 8.4.1 for exception for pre-dose orthostatic test at SV3). SAEs will be collected from signing of the ICF.	8.4
Adherence to regular medications confirmed			X	X	X	X	X	X		
Concomitant medications	X		X	X	X	X	X	X		6.9

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Clinic spirometry (post-BD)	X		X	X	X		X		Participants should bring their spirometer with them to all on-site visits. Screening spirometry at SV1 will be conducted using the spirometry equipment supplied to clinic. In the event that an adequate quality, maximal effort spirometry effort cannot be obtained at the first attempt during a study visit, a further reattempt is allowed (see Section 8.2.3).	8.2.3
Virtual spirometry (post-BD)			X	X	X		X			8.2.3
Provision and training on use of spirometer and e-Diary		X							Compliance to COPDCompEx (e-Diary) should be assessed at each study visit. Participants must demonstrate a compliance of at least 70% during the 14 days preceding SV3 to be eligible for randomisation.	8.2.3, 8.2.6
Assess adherence to the completion of e-Diary entries and home device use			X	X	X	X	X			

e-Diary and PEF (2 × daily recording) [c] D=distribute, R=Return		D	→	→	→	→	R		During the study treatment period, daily e-Diary compliance is critical for overall symptom rating, reliever medication use, and change in PEF. The investigator/authorised delegate should check the participant's adherence to the daily e-Diary at each visit and remotely at any time during the study. If it drops below 80% to 85%, sites should take steps to ask the participant about the reason and to encourage the participant to regularly complete the e-Diary. If compliance does not improve, or there is reason why the assessments cannot be completed (eg. temporary discontinuation or hospitalisation), the AstraZeneca study team should be contacted for discussion. Participants who fail to meet compliance rate may be rescreened once only. The baseline for COPDCompEx will be estimated during the period between SV2 and SV3. Participants should bring their spirometer and the device with the e-Diary on to all on-site visits. e-Diary and PEF will be recorded up until the day of SV7 or EDV.	
Cough VAS assessment		→	→	→	→	→	→		Cough VAS assessment will be recorded up until the day of SV7 or EDV.	8.2.4
CAT			X		X		X			8.2.5
EXACT			X		X		X			8.2.4
BCSS (daily)		→	→	→	→	→	→		BCSS (daily) assessment will be recorded up until the day of SV7 or EDV.	
Serum chemistry	X		X	X	X		X	X		8.3.4
T3, T4, TSH	X		X		X		X	X		
Systemic biomarkers of			X		X		X			8.8

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
cardiovascular comorbidities										
Blood sample for target engagement assay			X		X				Performed in a subsample of approximately 60 participants in selected countries.	8.6
Whole blood RNA PAXgene collection for mRNA analyses			X		X					8.8.1
Haematology	X		X	X	X		X	X		8.3.4
Plasma sample for proteomics			X		X					8.8.1

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
PK blood sampling for mitiperstat (AZD4831)			X (pre-dose)		X (pre-dose)		EDV only		In a subset of participants (approximately 20%), 2 additional post-dose samples will be collected at SV5. SV5 sample collection times are: pre-dose, 0.5 to 1.5 h, and 1.5 to 3 h, with a minimum of 1 hour between the post-dose sampling occasions. Once approximately 20% of participants have been tested, no further participants need this additional post-dose sampling. For participants who are discontinued from investigational product due to rash, a PK sample should be collected at the discontinuation Visit.	8.5.1
Exploratory biomarkers (blood)			X	X	X		X			8.8
Blood and urine sample for exploratory metabolite analysis							EDV only		Participants who discontinue study intervention due to rash or skin reaction only, at EDV.	8.8.1

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Genomics Initiative optional, exploratory genetic sample			X						Sample for genetic analysis can be taken at any visit.	8.7, Appendix D
Coagulation parameters	X									8.3.4
Blood sample for cell-free DNA analysis (optional)			X		X					8.8.2
Hepatitis B, C; HIV-1; virology	X									8.3.4
FSH (if needed to confirm post-menopausal status in female participants aged < 50 years)	X									8.3.4
Nasal mucosal lining fluid			X		X					8.8.1

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Spontaneous sputum			X		X				Collect sputum supernatant for target engagement and exploratory biomarkers. Sputum differential cell count should only be determined at SV3 (baseline) and only at sites with the appropriate equipment. Participants may use a flutter device (in clinic only) during sputum collection to make the sputum more accessible when they cough.	8.6, 8.8.1
Urinalysis	X		X					X		8.3.4
Study intervention dispensation			X	X	X					6
Study intervention dosing			←	Home administration once daily in the morning by the participant			→		Study intervention can be taken with or without food. On days with an on-site visit, participant should be dosed at the site during the visit.	5.3.1, 6

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Assess adherence to study intervention				X	X		X			
Return of all study supplies to clinic							X			
Cough Substudy Only										
Provision of and training of use of VitaloJAK® Cough Monitor device			X						Required only for participants of the cough substudy.	8.2.7
VitaloJAK® Cough Monitor 24-hour cough frequency			X		X					

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Q-SAW Substudy Only										
Qualitative semi-structured interviews			← X →						Two semi-structured interviews may be conducted up to 6 weeks apart. Required only for participants of the Q-SAW substudy at selected sites.	Appendix L
SPFQ Substudy Only										
SPFQ			X		X		X		Required only for participants of the SPFQ substudy at selected sites.	Appendix M
Patient Experience Interview Substudy Only										

Procedure	Screening (up to 28 days before Day 1)		Intervention Period					Follow-up Period	Notes	Details in protocol section or appendix
Visit	**SV1**	**SV2**	**SV3**	**SV4**	**SV5**	**SV6 (VV)[a]**	**SV7/ EDV [b]**	**SV8**	Study procedures should take place prior to dosing, unless specified otherwise. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV. See Section 7.1.4 for details of study end when the last participant has completed 12 weeks of treatment. Visits SV2, SV4, SV7/EDV, and SV8 are visits with a reduced number of assessments. SV6 is a virtual visit.	
Weeks	**-4**	**-2**	**1**	**4**	**12**	**18**	**24**	**+ 2 post-SV7/EDV**		
Visit Day (window) (days)	**-28 to -14**	**-16 to -14**	**1**	**28 (± 3)**	**84 (± 3)**	**126 (± 3)**	**168 (± 3)**	**+ 14 post-SV7/EDV (± 3)**	All Day 1 (SV3) assessments must be collected pre-dose unless otherwise stated. SV1 assessments may occur at any time during screening, including SV2, all must occur within the screening window. Informed consent must be obtained before any study procedure.	
Qualitative semi-structured interview				← X →					A semi-structured interview will be conducted in a subsample of participants, stratified over the study duration starting after at least 2 study visits, ie, after SV4. Required only for participants of the patient experience interview substudy at selected sites.	Appendix N

[a] For virtual visit of SV6, this will be conducted over telemedicine video conferencing facility based on technology provided by Zoom Inc (San Jose, California, USA), through the UNIFY platform, using a provisioned handheld device.

[b] SV7/EDV timepoint is SV7 or EDV. Participants discontinuing study intervention before SV7 should attend the site for SV7 assessments as soon as possible as an EDV.

[c] The morning and evening diaries that include cough VAS and BCSS start the day after SV2.

AE = Adverse event; BCSS = Breathlessness, Cough and Sputum Scale; BD = Bronchodilator; BP = Blood pressure; CAT = COPD Assessment Test; COPD = Chronic obstructive pulmonary disease; COPDCompEx = COPD Composite Exacerbations (composite measure of chronic obstructive pulmonary disease); CSP = Clinical Study Protocol; CT = Computed tomography; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; EDV = early discontinuation visit; EXACT = The Exacerbations of Chronic Pulmonary Disease Tool; FSH = Follicle stimulating hormone; ICF = Informed consent form; HIV = Human immunodeficiency disease; MPO = Myeloperoxidase; mRNA = Messenger ribonucleic acid; PEF = Peak expiratory flow; PK = Pharmacokinetic; Q-SAW = Qualitative; RNA = Ribonucleic acid; SAE = Serious adverse event; SPFQ = Study Participant Feedback Questionnaire; SV = Study visit; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid stimulating hormone; VAS = Visual analogue scale; VV = Virtual visit.

2 INTRODUCTION

Mitiperstat (AZD4831) is a potent, selective, irreversible, and dose-dependent inhibitor of MPO that is being developed for once daily treatment of COPD.

2.1 Study Rationale

This study will evaluate the efficacy and safety of the MPO inhibitor mitiperstat (AZD4831) in the treatment of moderate to severe COPD. Patients with COPD represent a huge unmet medical need: COPD exacerbations are associated with accelerated decline in lung function, high mortality, worsening quality of life and comorbidities, and high healthcare costs. In addition, COPD is also frequently associated with other metabolic or cardiovascular comorbidities, which also contribute to impaired quality of life and poorer survival. Furthermore, current COPD therapies, which include combinations of inhaled LABA, LAMA, and ICS, and add-on anti-inflammatory agents, do not eliminate symptoms, disability, exacerbations, or the hospitalisations that are associated with COPD, and do not significantly alter the course of COPD.

Preclinical smoke exposed animal models have shown that inhibition of MPO can halt the progression of emphysema and small airways remodelling (Churg et al 2012). In patients with COPD, higher sputum MPO is associated with increased risk of subsequent exacerbation of COPD, whilst a meta-analysis showed that sputum MPO levels are higher during exacerbation, compared to stable COPD. Persisting elevation of MPO during an exacerbation is associated with reduced response to therapy and more prolonged symptoms (Zhu et al 2014). Therefore, this study and the clinical development program for mitiperstat (AZD4831) will evaluate whether treating patients with COPD with mitiperstat (AZD4831) reduces exacerbations, and improves symptoms, quality of life, lung function, and other clinically relevant outcomes including comorbidities in patients with COPD.

2.2 Background

Chronic obstructive pulmonary disease is a common, chronic pulmonary disease which is characterised by airflow obstruction that is only partly reversible, and usually progressive and associated with a decline in lung function (Celli and Wedzicha 2019). Chronic obstructive pulmonary disease is now the third most common cause of death worldwide (WHO 2021). It is also associated with high morbidity and comorbidity and is currently the fifth leading cause of DALYs worldwide. Chronic obstructive pulmonary disease is also associated with an enormous economic burden, costing ~$50 billion in direct and indirect healthcare costs in the USA alone (Adeloye et al 2015).

Chronic obstructive pulmonary disease is caused by a complex interaction between genetics, early life, and ongoing environmental exposure. The major environmental risk factor is

inhaling cigarette smoke and/or other pollutants, which trigger a chronic inflammatory response in the lung that is associated with increased lung levels of oxidative stress and proteolytic injury leading to various pathologic changes in the lung that are heterogeneously expressed by patients. Patients with COPD can have varying combinations of destruction of the alveolar walls (or emphysema), small airway remodelling, and/or changes in the large airway (which manifests clinically as a frequent productive cough characteristic of the chronic bronchitis phenotype) that vary in severity between patients. The course of COPD can be punctuated by acute exacerbations of COPD which are defined as a sustained worsening of the patient's condition from the stable state, and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD. The initial exacerbation leading to hospitalisation in a patient with COPD is considered a seminal event for the patient as it heralds the onset of subsequent exacerbations that increase in frequency, and 50% of patients die within 3.6 years of their initial exacerbation (Suissa et al 2012).

In addition, COPD is also frequently associated with other metabolic or cardiovascular comorbidities, which also contribute to impaired quality of life and poorer survival. There is considerable overlap in the patterns of systemic vascular inflammation seen in COPD and that of advancing atherosclerotic disease and heart failure.

For these reasons, patients with COPD represent a huge unmet medical need.

Mitiperstat (AZD4831) is a potent, selective, irreversible, and dose-dependent inhibitor of MPO. Myeloperoxidase is a heme-containing enzyme that is stored within the granules of neutrophils. Myeloperoxidase catalyses the oxidation of halide ions by hydrogen peroxide leading to the generation of hypohalous acids which are potent oxidants. Under normal conditions, MPO and the hypohalous acids that it generates within neutrophil granules make crucial contributions to killing of phagocytosed bacteria. However, during excessive inflammation, neutrophil granule contents are extruded, and the extracellular hypohalous acids generated by MPO promote lung inflammation and injure the lung. Delivering an MPO inhibitor to guinea pigs that were exposed to cigarette smoke for 6 months reduced lung oxidative stress levels and lung inflammation and also halted the progression of emphysema and small airway fibrosis in the animals (Churg et al 2012) indicating that MPO activity contributes significantly to the pathogenesis of COPD-like disease in animals. MPO has also been linked to human COPD as MPO levels in sputum are elevated in patients with COPD versus controls and increase further during exacerbations (Zhu et al 2014). In addition, extracellular MPO serum levels are indirectly related to rate of decline in FEV1 (Park et al 2013). Finally, preliminary results for mitiperstat (AZD4831) in related cardiovascular studies have shown an acceptable benefit/risk profile of this compound and suggest potential benefits in comorbid conditions commonly associated with COPD. Thus, the clinical development program for mitiperstat (AZD4831) will evaluate whether treating

patients with mitiperstat (AZD4831) reduces exacerbations, and improves symptoms, quality of life, lung function and other clinically-relevant outcomes and comorbidities in patients with COPD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of mitiperstat (AZD4831) is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of mitiperstat (AZD4831) may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Identified and potential risks of mitiperstat (AZD4831), along with mitigation strategies, are shown in Table 2.

Table 2 Risk Assessment

Potential or identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention Mitiperstat (AZD4831)		
Identified risk		
Maculopapular rash	Generalised maculopapular rash has been observed in healthy volunteers in completed global SAD/MAD studies at single doses of 45 mg and above and at repeated doses of 15 mg and above, at 7 to 10 days post dose. In an MAD study in healthy Japanese and Chinese participants, maculopapular rash CTCAE Grade 1 has been reported in one PPD participant (of 6) on 5 mg mitiperstat (AZD4831); maculopapular rash Grade 2 in 3 PPD participants (of 6) on 10 mg mitiperstat (AZD4831), and maculopapular rash Grade 2 in 1 PPD participant (of 6) on 5 mg mitiperstat (AZD4831). One of 27 patients in the HfpEF study had generalised maculopapular rash CTCAE Grade 3 at 5 mg mitiperstat (AZD4831) occurring 5 days after up-titration from 2.5 to 5 mg.	The DRC will evaluate all cases of skin reaction/rash. The protocol clearly states the actions that have to be taken by the investigator, in case of maculopapular rash (see Appendix B, B 5).

Table 2 Risk Assessment

Potential or identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Potential risks		
Host defence impairment — infections (including pneumonia)	The MPO in neutrophils generates ROS that kill microorganisms so there is a theoretical risk that treatment with an MPO inhibitor could impair host-defence mechanisms. Kutter et al 2000 reported 7 life-threatening infections in MPO-deficient patients, of whom 3 had pneumonia. Pneumonia occurs commonly in patients with COPD and COPD is the strongest risk factor for development of pneumonia (Cavallazzi and Ramirez 2020). Humans with total or partial MPO deficiency generally do not have an increased susceptibility to infections but the incidence of *Candida* infections may be increased especially in patients with diabetes. Overall, invasive fungal infections such as candidaemia, disseminated infection, pneumonia, osteomyelitis, meningitis or liver abscess occur in fewer than 5% of MPO-deficient individuals (Antachopoulos 2010). An increased incidence of infection has not been seen with mitiperstat (AZD4831) in healthy volunteers/clinical study participants.	In order to adequately assess and characterise the risk of pneumonia in participants in a nonbiased manner, the DRC will review all AEs reported as pneumonia to ensure appropriate pre-defined and clinically consistent pneumonia criteria are met. Serious infections, including pneumonia, to be considered AESI.
Thyroid peroxidase inhibition (hypothyroidism)	In the preclinical safety studies in rats and dogs, inhibition of thyroid peroxidase caused reversible TSH increase, decreases in T4 and thyroid follicular cell hypertrophy. These effects have also been observed preclinically and clinically with other compounds of the same class and the magnitude of this effect is related to the degree of selectivity between MPO and TPO. Clinically relevant changes in thyroid parameters (TSH, T3, T4) have not been	Monitoring thyroid parameters (TSH, T3, free T4). Exclusion criterion 19.

Table 2 Risk Assessment

Potential or identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	seen in limited clinical data with mitiperstat (AZD4831).	
Blood pressure reduction and heart rate increase	In secondary pharmacology studies, mitiperstat (AZD4831) was shown to be an inhibitor of α1A adrenoceptors. Inhibition of this receptor is known to decrease BP and cause reflex tachycardia. Clinically relevant changes in BP/HR have not been seen in clinical study participants on mitiperstat (AZD4831).	Monitoring vital signs including orthostatic hypotension.
Anaemia and inflammation	One high-dose (150 mg/kg/day) dog developed severe clinical symptoms on Day 15 of dosing and did not recover sufficiently to allow further dosing. The dog was euthanised on Day 22. Haematology showed anaemia and inflammation. The cause of these findings is unknown. No other dogs in any studies with mitiperstat (AZD4831) showed similar symptoms or haematological changes. Clinically relevant haematological changes have not been seen in healthy volunteers/clinical study participants with mitiperstat (AZD4831).	Routine haematology monitoring.
Agranulocytosis and allergic reactions	Potential risk based on thiourea motif in the mitiperstat (AZD4831) molecule and is known liability for antithyroid drugs carrying the same motif. No consistent findings on haematological or bone marrow parameters in rats and dogs. Agranulocytosis has not been seen in healthy volunteers/clinical study participants with mitiperstat (AZD4831).	Routine haematology monitoring.

Table 2 Risk Assessment

Potential or identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Renal toxicity	A renal toxicity finding was found in transgenic RasH2 mice in the 1-month DRF study. Kidney findings included increased creatinine and BUN. Pathology showed discoloration/pale and enlarged kidney, increased kidney weight and histopathology showed renal degeneration/regeneration, tubular dilatation and granular casts. No kidney findings were observed at 125 mg/kg/day (NOAEL). Clinically relevant changes in kidney function have not been seen in clinical studies.	Exclusion criterion for eGFR < 30 mL/min/1.73 m^2 (exclusion criterion 20). Routine monitoring of renal function (creatinine).

AE = adverse event; AESI = adverse event of special interest; BP = blood pressure; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease; CTCAE = Common Terminology Criteria for Adverse Events; DRC = Data Review Committee; DRF = dose range-finding; eGFR = estimated glomerular filtration rate; HfpEF = heart failure with preserved ejection fraction; HR = heart rate; MAD = multiple ascending dose; MPO = myeloperoxidase; NOAEL = No-observed-adverse-effect level; ROS = reactive oxygen species; SAD = single ascending dose; T3 = triiodothyronine; T4 = thyroxine; TPO = thyroid peroxidase; TSH = thyroid stimulating hormone.

Appendix K includes an assessment of risks specific to the COVID-19 pandemic.

2.3.2 Benefit Assessment

Potential reduced hospitalisation

A reduced hospitalisation is considered to be a major potential benefit of the mitiperstat (AZD4831) treatment. Hospitalisation is a major challenge for all patients and many times patients suffer from life-threatening events, while being in a hospital.

Potential decrease in rate of exacerbations

Acute exacerbations of COPD are responsible for much of the hospitalisation-associated morbidity and mortality from COPD (Barnes et al 2015). It has been suggested that the mortality increases with the frequency of severe exacerbations (Soler-Cataluña et al 2005).

Potential quality of life improvement

Typical features of COPD include airway closure during expiration, which worsens on

exercise resulting in exertional dyspnoea and reduced exercise tolerance, and leads to marked impairment in quality of life. By improved lung function with mitiperstat (AZD4831) treatment, patients are expected to obtain a beneficial effect in their quality of life. It will be assessed in the Phase IIa study by the CAT for patients with COPD. Life expectancy is significantly limited in many patients and increased quality of life has a major role in potential benefits.

Potential improved symptom control

Symptom control will be evaluated by using the BCSS, EXACT, and cough frequency measurement. Improving BCSS and EXACT scores are considered to represent enhancement patients' daily life activities and will affect the quality of life.

Potential improved lung function

It is hypothesised that mitiperstat (AZD4831) will reduce airway inflammation and tissue damage. This could potentially lead to an improvement in lung function and/or reduce rate of decline in lung function. It would be of great clinical importance to prevent further decrease of lung function, especially in patients with severe COPD.

2.3.3 Overall Benefit/Risk Conclusion

COPD is a debilitating disease with high mortality that has a high unmet medical need. Therefore, it would be desirable to develop new anti-inflammatory treatments that affect chronic symptoms and disease progression in COPD. Exacerbations are major contributors to the increased rates of hospitalisation and mortality in patients with COPD. Two of the most important potential benefits are therefore decreasing the rate of exacerbations and reducing hospitalisation. Further, it is envisaged that mitiperstat (AZD4831) will improve symptom control and lung function. As a result of these potential benefits, patients' quality of life will likely be improved. The key risks include maculopapular rash and the potential risks host defence impairment-infections (including pneumonia) and thyroid peroxidase inhibition (hypothyroidism). Skin reactions (including maculopapular rash) and serious infections including pneumonia are AESIs; skin reactions and pneumonia will be evaluated by external experts. Given the available data and taking into account both the severity of COPD and that the patients to be included in the planned Phase IIa study have an advanced disease, it is considered that potential benefits outweigh the risks.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

Objectives	Estimand description[a]
Primary	
To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPDCompEx event in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arm. **Endpoint:** time to first COPDCompEx event. **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** Primary estimand: while on treatment – if an intercurrent event occurs before first COPDCompEx event, the participant will be censored at the time of intercurrent event. Supportive estimand: treatment policy (reflects ITT principle) – after intercurrent event participants remain in the study so that the endpoint can be observed. Treatment policy strategy used to estimate the efficacy of mitiperstat (AZD4831) in 'real-world' conditions.
Secondary	
To assess the PK of mitiperstat (AZD4831) in patients with moderate to severe COPD.	**Population:** all participants who had received at least one dose of mitiperstat (AZD4831), and who had at least one measurable PK sample post dose. **Endpoint:** plasma mitiperstat (AZD4831) concentration-time profiles during the intervention and follow-up periods, and PK parameters. **Population level-summary measure:** summary statistics. **Strategy for intercurrent events:** while on treatment.
To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first moderate or severe COPD exacerbation.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** time to first COPD exacerbation event[b] **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** while on treatment.

Table 3 Objectives and Endpoints

Objectives	Estimand description[a]
To assess the effects of mitiperstat (AZD4831) as compared to placebo on post-BD FEV1 in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in post-BD FEV1 after 12 weeks. **Population level-summary measure:** the difference in mean. **Primary estimand:** while on treatment. **Supportive estimand:** treatment policy.
To assess the effect of mitiperstat (AZD4831) compared with placebo on respiratory symptoms in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in EXACT, BCSS score, and Cough VAS at Week 12 and Week 24. **Population level-summary measure:** the difference in mean. **Strategy for intercurrent events:** while on treatment.
To assess the effect of mitiperstat (AZD4831) compared with placebo on disease impact in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in Total CAT measured in clinic at Week 12. **Population level-summary measure:** The difference in mean. Proportion of participants with change from baseline of -2 or less **Strategy for intercurrent events:** while on treatment.

Table 3 Objectives and Endpoints

Objectives	Estimand description[a]
Safety	
To assess the safety and tolerability of mitiperstat (AZD4831) compared with placebo in patients with moderate to severe COPD.	**Population:** all participants who received at least 1 dose of study intervention (Safety Analysis Set). **Endpoint:** safety and tolerability evaluations using AEs, SAEs, AESIs (skin reactions, including maculopapular rash, and serious infections, including pneumonia), vital sign measures, clinical laboratory assessments (clinical chemistry, haematology, and urinalysis), and ECG. **Population level-summary measure:** descriptive statistics eg, absolute counts and frequencies. **Strategy for intercurrent events:** Primary: while on treatment – if an intercurrent event occurs, any subsequent safety data will not be taken into consideration in the safety evaluation. Supportive: treatment policy – if an intercurrent event occurs, participants remain in the study and any safety data until Week 12 + safety follow-up will be taken into consideration in the safety evaluation.
Tertiary/Exploratory	
Objective	**Outcome Measure**
To assess the effect of mitiperstat (AZD4831) compared with placebo on biomarkers related to neutrophils and COPD disease activity.	• Sputum parameters including differential cell counts, and markers of neutrophil activation and inflammation. • MPO- and neutrophil- related circulating and nasal mucosal lining fluid biomarkers. • Putative biomarkers of lung tissue destruction and COPD disease progression. • Systemic biomarkers of cardiovascular comorbidities — including fibrinogen, hsCRP, IL-6, and NT-proBNP.
To assess the effects of mitiperstat (AZD4831) as compared to placebo on MPO activity and concentration in sputum and blood samples from patients with moderate to severe COPD.	Average change from baseline to Week 12 in MPO activity normalised to MPO concentration in sputum and ex-vivo-stimulated blood.

Table 3 Objectives and Endpoints

Objectives	Estimand description[a]
To assess the effects of mitiperstat (AZD4831) as compared to placebo on spirometry endpoints measured face-to-face and virtually in patients with moderate to severe COPD.	Spirometry endpoints, including but not limited to, FEV1, forced vital capacity, forced expiratory flow 25% to 75%, inspiratory capacity, and reproducibility.
To assess the effect of sputum MPO concentration at baseline on primary and secondary endpoints in patients with moderate to severe COPD.	Time to first COPDCompEx event in participants with low MPO concentration at baseline compared to high MPO concentration at baseline. Change from baseline post-BD FEV1 in participants with low MPO concentration at baseline compared to high MPO concentration at baseline.
Tertiary/Exploratory for Cough Substudy only	
To assess the effects of mitiperstat (AZD4831) compared to placebo on change in cough frequency measured over a 24-hour period between start of treatment and Week 12.	Change from start of treatment (SV3) in average 24-hour, waking, and sleeping cough frequency, using the VitaloJAK® Cough Monitor device, at Week 12.
To investigate whether cough frequency is associated with lung function (eg, PEF, FEV1), cough/COPD symptom scores (eg, BCSS, CAT and Cough VAS) and sputum/blood biomarkers (eg, MPO concentration, neutrophil activation markers).	Average cough frequency measured over a 24-hour period as measured at start of treatment (Visit SV3) and after 12 weeks treatment (Visit SV5) using the VitaloJAK® Cough Monitor device.

[a] An estimand is a precise description of the treatment effect reflecting the clinical question posed by the study objective. It summarises at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Definition from FDA E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials

[b] COPD Exacerbation: a worsening in the participant's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), may warrant a change in regular medication, and leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.
- Use of antibiotics to treat COPD exacerbation for at least 3 days.
- An inpatient hospitalisation due to COPD (defined as an inpatient admission ≥ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).
- Admission in emergency department or emergency room due to COPD for < 24 hours requiring intensive treatment.
- An episode of pneumonia.
- Results in death.

Moderate and severe COPD exacerbations are defined in Section 8.2.2.2.

Intercurrent events are events occurring after treatment initiation (eg, discontinuation of treatment, switching treatment, terminal events such as death) that affect either the measurement or interpretation of the summary measure (eg, hazard ratio) associated with the clinical question of interest.
This study contains 2 intercurrent events:

1 Treatment discontinuation (with the following reasons: SAE, death not due to exacerbation, COVID-19, pneumonia, other).
2 Prohibited medication.

- AE = adverse event; AESI = adverse event of special interest; BCSS = Breathlessness, Cough and Sputum scale; BD = bronchodilator; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; COPDCompEx = COPD Composite Exacerbations; COVID-19 = Coronavirus disease 2019; ECG = electrocardiogram; EXACT = The Exacerbations of Chronic Pulmonary Disease Tool; FDA = Food and Drug Administration; FEV1 = forced expiratory volume in 1 second; hsCRP = high sensitivity C-Reactive Protein; IL-6 = interleukin-6; ITT = intent-to-treat; MPO = myeloperoxidase, NT-proBNP = N-terminal pro-brain natriuretic peptide; PEF = peak expiratory flow; PK = pharmacokinetic; SAE = serious adverse event; SV = study visit; VAS = visual analogue scale.
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The objectives of the Q-SAW, SPFQ, and patient experience interview substudies are detailed in Appendix L, Appendix M, and Appendix N, respectively.

4 STUDY DESIGN

4.1 Overall Design

A schematic is provided in Section 1.2 showing the overall study design.

This is a Phase IIa, randomised, placebo-controlled, double-blind, parallel-arm, event-driven study with an up to 24-week treatment time. It will be performed in approximately 100 sites across approximately 14 countries. It is designed to evaluate the efficacy and safety of mitiperstat (AZD4831) administered QD using a tablet in adult participants with confirmed moderate to severe symptomatic COPD (FEV1/FVC < 0.7, ≥ 10 pack-years smoking history, and post-BD FEV1 ≥ 25% predicted) who are at high risk of exacerbations despite being maintained on optimised SoC inhaled therapies — triple inhaled therapy (ICS + LABA + LAMA) or ICS + LABA dual therapy or LABA + LAMA dual therapy for participants who are deemed unsuitable for ICS. The treatment will be over a minimum 12-week and maximum 24-week period.

- Approximately 677 participants will be screened and 406 participants randomised into the study to evaluate mitiperstat (AZD4831) 5 mg QD versus placebo.
- Being at high risk of exacerbations is defined as participants fulfilling one or more of the following criteria:
  - ≥ 1 moderate or severe exacerbation in the last 2 years (defined as requiring systemic corticosteroids and/or antibiotics for at least 3 days duration [or 1 injection of depot formulation], or hospitalisation for reason of AECOPD in the 24 months prior to screening; see Section 5.1).
  - Frequent productive cough (see Section 5.1).
  - Post-BD FEV1 of < 50% predicted.
- Participants will be randomised 1:1 to mitiperstat (AZD4831) 5 mg QD or placebo QD.
- Randomisation will be stratified by country.
- The primary objective is to evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPDCompEx event in patients with moderate to severe COPD. The primary endpoint will be time to first COPDCompEx event.
- Secondary assessments of efficacy include: time to first COPD exacerbation event, post-BD FEV1 at Week 12 compared to Week 1, MPO level and activity in sputum at Week 12 compared to baseline, and symptom scores.
- The study will explore an alternative community-based patient recruitment in some countries, utilising a network of Primary Care and Community COPD/Pulmonary Rehabilitation facilities to boost enrolment. The target countries with established Community COPD Clinic/Pulmonary Rehabilitation infrastructure will serve as participant recruitment centres or new sites.

- Enrolment will be stopped after at least 194 first COPDCompEx events have occurred. At this point, all participants enrolled in the study that have not yet completed SV5 should continue in the study to complete 12 weeks of treatment. For these participants SV5 and SV7 should be combined into one visit. Participants who have already completed 12 weeks of treatment when study enrolment is stopped should attend SV7 as soon as possible, continuing treatment until they do. All participants should attend SV8 14 ± 3 days after SV7/EDV.
- The URC will review efficacy data from the IA and the DRC will perform periodic safety monitoring with a focus on skin reactions and pneumonia. See Appendix A 5 for details.
- To reduce the burden on participants, Visits SV2, SV4, SV7, and SV8 will have a limited number of assessments and shortened duration, and Visit SV6 will be a "virtual visit" which will be performed away from the study site. This will be conducted over the same telemedicine video conferencing facility that is being used for the virtual spirometry during other visits in the study and is based on technology provided by Zoom Inc (San Jose, California, USA), through the UNIFY platform, using a provisioned handheld device.
- The entire study period is planned to take between 18 and 30 weeks for each individual participant: a 4-week screening period, minimum 12 weeks to a maximum 24 weeks of dosing and 2 weeks of follow-up.

4.1.1 Cough Monitoring Substudy

A cough monitoring substudy will be performed alongside this study. In the cough substudy, a subset of participants (up to approximately 50 participants from each arm) from selected sites will be included. Twenty-four-hour cough frequency monitoring will be conducted at Visit SV3 (start of treatment) and Visit SV5 (after 12 weeks of treatment) using the VitaloJAK® Cough Monitor device. The main objective of the substudy is to explore the effect of mitiperstat (AZD4831) compared with placebo on change in average 24-hour, awake, and sleeping cough frequency between baseline and Week 12. The substudy will also investigate whether average cough frequency is associated with lung function (eg, PEF or FEV1), cough/COPD symptom scores (eg, BCSS, CAT, and cough VAS) and sputum/blood biomarkers (eg, MPO concentration, neutrophil activation markers).

4.1.2 Q-SAW Substudy

The Q-SAW substudy will be performed alongside this study. A subset of approximately 40 participants in total, from selected sites in selected countries will be included.

COPDCompEx captures AWEs ie, clinically relevant deteriorations of PEF, reliever use or symptoms that fulfil specific criteria in terms of reaching thresholds or slopes. The Q-SAW

substudy aims to provide a deeper understanding of day-to-day variations in symptoms and the impact of AWEs on the patient's life.

Participants may be invited to 2 semi-structured interviews: an initial interview and a second interview up to 6 weeks later, each conducted over video or telephone call.

For further details on the Q-SAW substudy, refer to Appendix L.

4.1.3 SPFQ Substudy

The SPFQ substudy will be performed alongside this study. Participants from selected sites in selected countries will have the option to provide feedback on their clinical study experience. Participants will complete the SPFQ in electronic format on the UNIFY platform at SV3, SV5, and SV7, using a provisioned handheld device. The aim of the substudy is to gain an understanding of patient experience in clinical studies and identify where improvements can be made in the clinical study process.

For further details on the SPFQ substudy, refer to Appendix M.

4.1.4 Patient Experience Interview Substudy

The patient experience interview substudy will be performed alongside this study and the data from this qualitative substudy will complement the data from the quantitative SPFQ (Section 4.1.3). In the patient experience interview substudy, approximately 20 participants in total, from selected sites in selected countries will be invited to attend a remote, semi-structured interview conducted over video call or telephone call. The aims of the substudy are to understand how participant experience can be improved and to gain further insight into the participant perceptions and experiences of the digital technology used, including the virtual spirometry.

For further details on the patient experience interview substudy, refer to Appendix N.

4.1.5 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 SARS-CoV-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 AstraZeneca 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 minimise 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).
- 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 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.

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

4.1.6 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 HCPs involved in the clinical study 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 AstraZeneca 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.

Applicable measures for source data verification, if on-site monitoring at the study sites is not indicated due to the COVID-19 pandemic, should be implemented.

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

4.2 Scientific Rationale for Study Design

This Phase IIa study has 2 treatment arms (mitiperstat [AZD4831] and placebo) to allow the efficacy and safety of mitiperstat (AZD4831) to be assessed. Participants will remain on their SoC treatment (triple or dual therapy) during the study.

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. It is considered the optimal approach according to ICH E9 "Statistical principles in clinical studies" (ICH 1998). The inclusion of a placebo arm is also recommended by the EMA guideline EMA/CHMP/483572/2012 "Clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD)" (EMA 2012) for drugs to be used as add-on therapy, providing that all participants receive optimised background therapy; participants in both groups will remain on SoC inhaled therapies (triple inhaled therapy [ICS + LABA + LAMA] or ICS + LABA dual therapy or LABA + LAMA dual therapy for participants who are deemed unsuitable for ICS).

The primary endpoint, time to COPDCompEx event, is a novel, surrogate, composite endpoint that captures clinically relevant deteriorations (diary events [eg, PEF], reliever use, symptoms, exacerbation events, and study dropouts resulting from a lack of efficacy) that fulfil specific criteria in terms of changes from baseline and deterioration over 5 days, combined with exacerbations. Three-month COPDCompEx treatment effects have been shown to reflect treatment effects on exacerbations at 6 to 12 months (Vogelmeier et al 2020).

The participants anticipated to be most likely to benefit from mitiperstat (AZD4831) treatment are those at high risk of exacerbations. Therefore, participants will be at high risk of exacerbations as defined by the criteria in Section 4.1.

The study is event-driven: once at least 194 COPDCompEx first events have occurred, enrolment will stop (see Section 7.1.4).

The study design includes several outcome assessments that will be performed remotely by participants. The purpose of this is to enable more frequent measurement and to minimise the burden of attending on-site visits. Several of these measurements will undergo further validation during the course of the study to ensure equivalence with site-based assessments where appropriate.

4.2.1 Patient Input into Design

Two patient experts with COPD have been engaged to provide input into the study objectives and design. Their advice has been actively considered and incorporated where appropriate. In particular they have influenced the duration, acceptability, and burden of study visits; the

devices and setting for clinical outcome assessments; and practical aspects of safety monitoring.

Their input and advice will continue during the course of the study setup, providing further feedback and perspectives on protocol implementation.

In addition, a wider group of volunteer patients will be engaged to pilot the usability and acceptability of the planned digital health devices prior to study initiation.

4.3 Justification for Dose

The dose selection is based on target engagement (MPO inhibition) data from the Phase I MAD study (D6580C00004), the Phase IIa study (D6580C00003), and data from the MAD study in Japanese and Chinese healthy participants (Study D6580C00008). One dose level is being proposed (5 mg) based on expected efficacy and safety. The 5 mg dose is predicted to be a clinically relevant dose in COPD, resulting in approximately 56% MPO inhibition, based on PK/PD data from the Phase I and Phase II studies.

Four Phase I clinical studies have been completed in which a total of 36 healthy subjects have been exposed to mitiperstat (AZD4831) at doses 5 to 405 mg as single doses and 53 healthy subjects (including 24 Japanese and Chinese participants) at doses 2.5 to 45 mg as multiple doses.

In these healthy subjects, mitiperstat (AZD4831) was generally well tolerated with the exception of generalised maculopapular rash seen around 7 to 10 days after the first dose. Maculopapular rash CTCAE Grade 1 was reported in 1 of 6 PPD participants on 5 mg mitiperstat (AZD4831); Grade 2 maculopapular rash was reported in 1 of 6 PPD participants on 5 mg mitiperstat (AZD4831).

A Phase IIa study in participants with HfpEF was prematurely terminated during the COVID-19 pandemic after meeting pre-defined target engagement, safety, and tolerability criteria (Study D6580C00003). One of 27 participants receiving 5 mg mitiperstat (AZD4831) was discontinued from study treatment due to CTCAE Grade 3 generalised maculopapular rash.

4.4 End-of-Study Definition

For the purpose of Clinical Trial Transparency (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 they have completed all phases of the study including SV8.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be 40 to 80 years of age inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2 Participants who have a confirmed primary diagnosis of moderate to severe COPD as per GOLD criteria (FEV1/FVC < 0.7, and post-BD FEV1 ≥ 25% predicted) (Global Initiative for Chronic Obstructive Lung Disease 2022).

3 Participants who are current or ex-smokers with a tobacco history of ≥ 10 pack-years.

Pack-years are calculated as average number of cigarettes per day × number of years / 20. For example, 1 pack-year = 20 cigarettes smoked per day for 1 year or 10 cigarettes per day for 2 years.

4 Participants must be deemed at high risk of exacerbations as defined by any one of the following:

(a) A documented history of ≥ 1 moderate or severe AECOPD requiring systemic corticosteroids and/or antibiotics for at least 3 days' duration (or 1 injection of depot formulation), or hospitalisation for reason of AECOPD in the 24 months prior to screening. A verbal history from the participant of AECOPD is not sufficient. Acceptable documentation is:

- Clinic visit or consultation (primary or specialist HCP) notes or emergency room/hospital records providing evidence of ≥ 1 moderate or severe AECOPD in the previous 24 months prior to enrolment
- Documented prescription of systemic corticosteroids of at least 3 days' duration (or 1 injection of depot formulation) and/or antibiotics for treatment of an AECOPD event. In participants with an established self-management plan, documented filling of a prescription to replace an above course of therapy will be considered as adequate
- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant was hospitalised or treated with systemic corticosteroids or antibiotics for a COPD exacerbation, or

(b) Frequent productive cough, defined as a positive response to both of the following questions:[*]

- Over the past 3 months, I have coughed at least several days a week
- Over the past 3 months, I have brought up phlegm (sputum) at least several days a week, or

(c) Post-BD FEV1 < 50% predicted.

5 Participants who have a documented stable regimen of triple therapy or dual therapy for ≥ 3 months prior to enrolment (change of inhaler device or change of medication in the same drug class is allowed). Triple therapy may consist of an appropriate combination of ICS + LABA + LAMA. Dual therapy consists of either inhaled ICS + LABA or LABA + LAMA where the treating physician deems the participant unsuitable for ICS (eg, blood eosinophil count ≤ 100 cells/µL on 2 separate occasions, or on the basis of previous or perceived risk of significant AEs from ICS-based therapy, such as previous episodes of pneumonia or significant oral candidiasis).

- Both dual and triple therapy may be in the form of separate inhalers or fixed dose combination inhalers but may not be in nebulised form. Documented evidence of prescription for these medications must be provided. A verbal history from the participant is not considered sufficient.
- Acceptable documentation includes:

[*] Used with the permission of the St. George's Respiratory Questionnaire Steering Committee.

- Recent, active medication list as per HCP note
- Filled prescriptions based on a pharmacy record
- Another acceptable medical record as per local clinical practice

6 Participants who are clinically stable and free from an exacerbation of COPD for 1 month prior to SV1 (screening) and prior to Day 1.

7 Participants who are at least 70% compliant with each of the following: morning e-Diary, evening e-Diary, and PEF measurements during the 14 days preceding SV3 based on the e-Diary. This is defined as completing the daily diary for any 10 mornings, any 10 evenings, and performing PEF for any 10 morning and any 10 evenings.

8 Participants who are able to read, write, and use electronic devices.

Weight

9 Body mass index within the range 18 to 40 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

10 Male or female of non-childbearing potential.

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

(a) Male participants:

- Male participants must be surgically sterile (eg, vasectomy with confirmed azoospermia) or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides if available) during treatment and until the end of relevant systemic exposure in the male participant, plus a further 105 day period. Male study participants must not donate or bank sperm during this same time period.
- For a non-pregnant woman of childbearing potential partner, contraception recommendations should also be considered. Acceptable methods of contraception are birth control pills, injections, implants, or patches, intrauterine devices, and tubal ligation/occlusion. A barrier method is not necessary if the female partner is sterilised. All other contraceptive methods are considered unacceptable.

(b) Female participants must not be lactating and must be of nonchild-bearing potential. Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy [but not tubal ligation]), or who are 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 follicle stimulating hormone 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.

Informed Consent

11 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.

5.2 Exclusion Criteria

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

Medical Conditions

1 This criterion has been removed.

2 Participants with a significant COVID-19 illness within 6 months of enrolment defined as:

(a) A diagnosis of COVID-19 pneumonia based on radiological assessment.

(b) A diagnosis of COVID-19 with significant new findings from pulmonary imaging tests.

(c) A diagnosis of COVID-19 requiring hospitalisation and/or oxygen supplementation therapy.

3 As judged by the investigator, any evidence of any active medical or psychiatric condition or other reason (at SV1 [screening] through to SV3 [pre-dose]) which in the investigator's opinion makes it undesirable for the participant to participate in the study.

This includes but is not limited to:

(a) Diabetes mellitus, except for participants with type 2 diabetes mellitus who are well controlled (ie, HbA1c < 10%).

(b) History of left heart failure (left ventricular ejection fraction < 40% on echocardiogram or Cardiac magnetic resonance imaging).

(c) Unstable angina, acute coronary syndrome/acute myocardial infarction or coronary intervention with percutaneous coronary intervention/coronary artery bypass graft within 6 months, arrhythmia requiring treatment, or cardiomyopathy.

(d) Clinically significant aortic stenosis.

(e) Systemic hypertension, except if well controlled and stable for at least 3 months in the opinion of the investigator.

(f) Pulmonary arterial hypertension, either idiopathic or due to connective tissue or thromboembolic disease. Participants with cor pulmonale (with or without long term oxygen supplementation) secondary to severe COPD are allowed.

(g) History of another underlying condition that predisposes the participant to infections. This includes but not limited to history of splenectomy, history of previous systemic fungal infection or known primary or secondary immune deficiency syndromes (including but not limited to chronic granulomatous disease, severe combined immunodeficiency, chronic mucocutaneous candidiasis, hyper-IgE syndrome, myeloperoxidase deficiency, leukocyte adhesion deficiency, DiGeorge syndrome, X-linked hyper-IgM syndrome, Wiskott-Aldrich syndrome and common variable immunodeficiency).

(h) History of ulcerative colitis, Crohn's disease, or microscopic colitis diagnosed by either a gastroenterologist or by histopathology.

4 Current diagnosis of asthma or past diagnosis of asthma which persisted beyond the age of 25 years. A misdiagnosis of asthma is not exclusionary if any of the following are met:

(a) A diagnosis of asthma that was, within 2 years of original diagnosis of COPD, determined to be a misdiagnosis by the physician treating at the time.

(b) A brief episode of asthma-like symptoms without longer-term asthma treatment confirmed by the investigator to be a misdiagnosis.

(c) A diagnosis of asthma made when the participant was aged ≥ 40 years, confirmed by the investigator to be a misdiagnosis on the basis of objective testing.

5 Clinically important pulmonary disease other than COPD (eg, active lung infection, clinically significant bronchiectasis where bronchiectasis is the predominant diagnosis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha-1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome), radiological findings, and/or laboratory findings suggestive of a respiratory disease other than COPD that is contributing to the participant's respiratory symptoms.

6 Known history of allergy or reaction to any component of the study intervention formulation, including hereditary fructose intolerance.

7 Any other clinically relevant abnormal findings on physical examination, laboratory testing including haematology, coagulation, serum chemistry, or urinalysis; or recent lung imaging prior to randomisation, which in the opinion of the investigator or medical monitor may compromise the safety of the participant in the study or interfere with evaluation of the study intervention or reduce the participant's ability to participate in the study. In addition, if a participant meets any of the criteria below, they will be excluded from the study:

(a) ALT or AST > 2 × ULN.

(b) TBL > 2 × ULN (unless due to Gilbert's disease).

(c) Evidence of chronic liver disease on previous hepatic imaging or pathological sampling.

(d) Abnormal vital signs, after 10 minutes of being in a comfortable supine position (confirmed by 1 controlled measurement), defined as any of the following:

(i) Systolic BP < 90 mmHg or ≥ 160 mmHg.

(ii) Diastolic BP < 50 mmHg or ≥ 95 mmHg.

(iii) Pulse < 45 or > 100 beats per minute.

(e) Signs of pulmonary oedema or volume overload.

(f) Any clinically significant rhythm, conduction, or morphology abnormalities in the 12-lead ECG including but not limited to corrected QT interval (Fridericia) (Vandenberk et al 2016) > 450 ms. Participants with atrial fibrillation or flutter and optimally controlled ventricular rate at resting < 100 beats per minute might be included as judged by the investigator.

(g) Recent lung imaging that requires immediate diagnostic investigation or follow-up. If initial repeat surveillance imaging has been undertaken, and the abnormality is considered low risk of malignancy, the participant may be eligible for enrolment following confirmation with the AstraZeneca medical monitor.

8 History of a clinically significant infection (viral, bacterial, or fungal; defined as requiring systemic antibiotics, antiviral, or antifungal medication for > 7 days) within 4 weeks prior to SV3 (Day 1) (including unexplained diarrhoea) or clinical suspicion of infection at time of dosing.

9 Any history of lung volume reduction surgery, including endoscopic lung volume reduction procedure with endobronchial valves.

10 Use of domiciliary non-invasive positive pressure ventilation device, including BiPAP. CPAP for the purpose of treating obstructive sleep apnoea is allowed.

11 Active malignancy requiring treatment (with the exception of basal cell or squamous cell carcinomas of the skin and stable prostate cancer)

12 Active drug-induced hypersensitivity skin reaction or history of SCARS (including DRESS, SJS/TEN, and AGEP).

13 History of ANCA positive vasculitis or ANCA positive skin disease.

14 History of, or a reason to believe a participant has a history of, drug or alcohol abuse within the past 2 years prior to screening.

15 Positive hepatitis C antibody, hepatitis B virus surface antigen, or hepatitis B virus core antibody, at screening.

16 Known to have tested positive for HIV, including at screening.

17 Evidence of untreated active TB:
- Participants currently receiving treatment for active TB may be considered after completion of an appropriate course of therapy.

18 Change in smoking status in 12 weeks prior to enrolment or intention to change smoking status between enrolment and end of follow-up.

19 Current diagnosis of hyperthyroidism, uncontrolled hypothyroidism (including but not limited to TSH ≥ 10 mIU/L), or any clinically significant thyroid disease.

20 Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration formula at screening.

Prior/Concomitant Therapy

21 Participants currently receiving background therapy for COPD that is not approved by regulatory authorities in the country of study (with the exception of nicotine vaping products, long-term azithromycin, erythromycin and/or ICS standalone inhaler [as part of triple or dual therapy] of at least 3 months' duration) are not eligible for the study.

22 This criterion has been removed.

23 Major surgery within 8 weeks prior to screening or planned inpatient surgery or hospitalisation during the study period.

24 Treatment with broad spectrum antibiotic (excluding long-term azithromycin or erythromycin as mentioned in exclusion criterion 21) within 4 weeks prior to randomisation (Day 1).

25 Donation of blood or blood products in excess of 500 mL within 3 months prior to screening.

26 History of allogeneic bone marrow transplant.

27 Participant who is going to start or finish intensive COPD rehabilitation program at any time during study period. Participants can be recruited immediately following the completion of their COPD rehabilitation program.

28 Receiving any of the prohibited concomitant medications as specified in the CSP:
(a) Acute systemic (oral or injectable) corticosteroids within 4 weeks of SV1.
(b) Chronic oral steroids within 6 months of SV1.
(c) Any other immunosuppressive therapy (including methotrexate, cyclosporine, tacrolimus, or maintenance systemic steroid treatment) within 3 months of randomisation.
(d) Immunoglobulin or blood products within 4 weeks of SV1.
(e) Live, attenuated, or mRNA vaccines within 2 weeks prior to SV1 only.
(f) Interferon gamma within 3 months of randomisation.

(g) Investigational products within 4 months or 5 half-lives of randomisation, whichever is longer.

(h) Marketed biologics within 4 months or 5 half-lives of randomisation, whichever is longer.

(i) Sulfamethoxazole, sulfadiazine, and dapsone, from 14 days before randomisation until 14 days after last dose of study treatment.

(j) Propylthiouracil, carbimazole, and methimazole.

29 Any concomitant medications known to be potent CYP3A4 inducers or inhibitors from 14 days before randomisation until 2 days after the last dose of study treatment (see Table 8), eg, itraconazole, rifampicin, or clarithromycin.

30 Initiation within 2 months prior to study start or during the study initiation of a new treatment by allopurinol, lamotrigine, and phenytoin. All of them commonly cause rash.

Prior/Concurrent Clinical Study Experience

31 Concurrent enrolment in another clinical study involving an investigational treatment.

Other Exclusions

32 Participant is an investigator, sub-investigator, study coordinator, or employee of the participating site or AstraZeneca, or is a first-degree relative of the aforementioned.

33 Inability to perform technically acceptable spirometry.

34 Randomisation of participant is not permitted due to closure of stratum.

35 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.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

1 Participants should avoid eating a large meal for at least 1 hour prior to all scheduled supervised spirometry assessments.

2 Participants should refrain from consumption of grapefruit juice and St John’s wort from the start of study intervention until the final dose. Study intervention can be taken with or without food.

5.3.2 Alcohol and Tobacco

1 Chronic alcohol or drug abuse within 2 years (at the investigator’s discretion) is restricted prior to SV1 and throughout the conduct of the study.

Current tobacco smokers or prior tobacco smokers, with smoking history ≥ 10 pack-years (1 pack-year = 20 cigarettes smoked per day for 1 year) at SV1 are allowed. Never smokers are not allowed to enter the study. Any change in smoking status in the 12 weeks prior to enrolment or intention to change smoking status between enrolment and the end of follow-up will result in a screen failure. However, following change in smoking status, they will be eligible for rescreening. Smoking status changes during the study will be captured on the eCRF but the participant will be permitted to continue in the study.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently 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, if one or more of the following occurs:

- There is reason to believe the reason for ineligibility was temporary (eg, exacerbation and/or background medication stability periods).
- Failure to achieve the required 70% compliance on any of the following: morning e-Diary, evening e-Diary, and PEF measurements during the 14 days preceding SV3.
- Any change in smoking status in 12 weeks prior to enrolment or intention to change smoking status between enrolment and end of follow-up will result in a screen failure. However, following a change in smoking status, participants will be eligible for rescreening.

Only one rescreening per participant is allowed in the study, when there is a reasonable expectation that the participant will become eligible for the study. Prior to rescreening, participants must be reconsented. Rescreened participants should be assigned the same participant number as for the initial screening.

Where an appropriate chest CT scan was performed within the last 6 months, such as for part of the previous screening process, this CT scan may be used for the study. This scan should be submitted at the time of screening, but can be repeated if the quality is not adequate for analysis.

If previously performed as part of the previous screening process, a second FSH test does not need to be performed. All other tests must be performed as per the SoA (Table 1).

5.5 Criteria for Temporarily Delaying Enrolment, Randomisation, or Administration of Study Intervention

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, IMPs and NIMPs, medical devices and other interventions (eg, surgical and behavioural) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Table 4 Study Interventions

Arm name	Mitiperstat (AZD4831)	Placebo
Intervention name	Mitiperstat (AZD4831)	Placebo
Type	Drug	Placebo
Dose formulation	Film-coated tablet	Film-coated tablet
Unit dose strength	5 mg	N/A
Dosage level	5 mg once daily Home administration by the participant should be in the morning. On days with an on-site visit, participant should be dosed at the site during the visit.	Once daily Home administration by the participant should be in the morning. On days with an on-site visit, participant should be dosed at the site during the visit.
Route of administration	Oral	Oral
Use	Experimental	Placebo-comparator
IMP or NIMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	Provided centrally by AstraZeneca
Packaging and labelling	Study Intervention will be provided in bottles. Each bottle will be labelled in accordance with GMP and country regulatory requirements for labelling.	Study Intervention will be provided in bottles. Each bottle will be labelled in accordance with GMP and country regulatory requirements for labelling.
Current/former name(s) or alias(es)	N/A	N/A

GMP = Good manufacturing practice; IMP = Investigational Medicinal Product; N/A = not applicable; NIMP = Non-Investigational Medicinal Product

6.1.1 Medical Devices Including Combination Products with a Device Constituent

1) Medical devices (not manufactured by or for AstraZeneca) provided for use in this study are:
    - MIR Spirobank Smart spirometer (available in each study region)
    - MIR Spirobank II Smart (available in each study region) (SV1 screening visit only)
    - VitaloJAK® Cough Monitor (available in each study region where the cough substudy will be performed)
2) Instructions for medical device use are provided.
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 8.4.13) and appropriately managed by AstraZeneca.

In addition to the medical devices described above, an e-Diary (a handheld device) will be used to complete the assessments described in Section 8.2.6. AstraZeneca's UNIFY application will be used on the handheld device for collection of e-Diary, PEF, and virtual spirometry data. The Medidata application for image handling is installed on the handheld device. A tablet installed with ZEPHYRx's application will display the data from the MIR Spirobank II Smart.

ArtiQ.QC will be integrated into ZEPHYRx application for an instant artificial intelligence-based over-reading of spirometry against ATS/ERS 2019 standards. Meanwhile ArtiQ.RBM software will also be utilised in ZEPHYRx and UNIFY, for risk-based quality management analysis of spirometry and identification of sites that may require quality improvement initiatives.

Both ArtiQ.QC and ArtiQ.RBM are not considered to meet the definition of a medical device as it only performs quality control and quality management functions. It will not be used as the basis for any clinical decision making or patient treatment.

The UNIFY application is not considered to meet the definition of a medical device as it performs only administrative study functions and collects and displays medical information. It does not process or analyse medical information for the purposes of treating or diagnosing participants.

The ZEPHYRx application is not considered to meet the definition of a medical device as it does not modify or alter the medical device data coming from the spirometer. The application will only be used for assessing if the participant meets the screening criteria for the study. It will not be used as the basis for any clinical decision making or patient treatment.

The Medidata application is not considered to meet the definition of a medical device as it only acts as a file transfer mechanism. The images captured in the application are not used for clinical decision making or patient treatment.

6.2 Preparation, Handling, Storage, and Accountability

- The investigator or designee (eg, pharmacist or study coordinator) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).
- Only participants randomised 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.
- 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).
- Study medication will be dispensed to participants in bottles. Participants will be instructed to take one tablet per day in the morning.
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomised study intervention, and have an E-code assigned, using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM) system. Before the study is initiated, the log in information and directions for the IRT/RTSM will be provided to each site.

Participants will be randomised 1:1 to mitiperstat (AZD4831) 5 mg or placebo at SV3 (Table 1). Randomisation will be stratified by country.

Study intervention will be dispensed at the study visits summarised in the SoA (Table 1).

Returned study intervention should not be re-dispensed to the participants.

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number

to be allocated to the participant at the dispensing visit.

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

6.4 Blinding

The study will be blinded to both participants and investigators/site staff as well as to AstraZeneca staff. With the formation of the URC and DRC (see Appendix A 5) the study will become unblinded to the AstraZeneca staff assigned to these committees (including those with clinical, medical, statistical, and programming expertise) who will form a firewalled URC for administrative purposes and will all be independent from the study team (see Appendix A 5). The URC will be responsible for conducting the administrative IA whereas the DRC will be responsible for safety monitoring.

The randomisation list should be sent to the personnel analysing the PK samples. Pharmacokinetic samples will be analysed by the bioanalytical laboratory performing the bioanalyses only for participants on active treatment, as referenced in Section 8.5.2. To allow for the appropriate selection of samples, the bioanalytical laboratory will, therefore, have access to the treatment codes but will not share the codes with AstraZeneca or others involved in the study until the blinding is broken for the study.

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 investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the 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 an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

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 intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant’s intervention assignment is unblinded, AstraZeneca must be notified within 24 hours after breaking the blind.

6.5 Study Intervention Compliance

The first dose of study intervention will be administered in clinic on the day of randomisation. Participants will receive study intervention at the site on visit days and at home between visits.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. 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.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and comparison of this data to e-Diary self-administration data, and/or direct questioning can be used to confirm details. Compliance will be documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of the mitiperstat (AZD4831)/placebo tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the eCRF.

6.6 Dose Modification

No dose modifications are allowed during the study.

6.7 Continued Access to Study Intervention After the End of the Study

There is no planned intervention following the end of the study.

6.8 Treatment of Overdose

For this study, any dose of mitiperstat (AZD4831) greater than those specified in this protocol within the same day will be considered an overdose.

Should an overdose occur, the patient should be treated symptomatically, and supportive measures instituted.

In the event of an overdose, the investigator should:

- Evaluate the participant to determine, in consultation with the Study Physician, if possible, whether study intervention should be interrupted.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.4.12 for details of AE/SAE reporting related to overdose.
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Prior and 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

If and when a participant received a COVID-19 vaccination, the following information (if available) should be recorded in the participant notes:

- Brand name (or alternatively name of manufacturer)
- Date of administration
- Whether dose was first, second, or booster dose
- Dose
- Anatomical site/region of administration (eg, left deltoid)
- Lot number

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

The following medications are prohibited (see Section 5.2 for details of duration of prohibition):

- Potent inhibitors or inducers of CYP3A: mitiperstat (AZD4831) is metabolised via CYP3A4 and hence strong inhibitors or inducers of CYP3A should not be administered from 14 days before randomisation until 2 days after the last dose of study treatment since that will affect the plasma concentration of mitiperstat (AZD4831). For guidance regarding potential interactions with concomitant medications that are inhibitors or inducers of CYP3A4, see Appendix F, Table 8.
- Treatment with allopurinol, lamotrigine, and phenytoin should not be initiated within 2 months prior to study start or during the screening and treatment period. All of them commonly cause rash. They were also recently shown (in a large population database) to

be associated with the highest absolute risk for life-threatening SJS and TEN among various culprit drugs (Gronich et al 2022).

- Acute or chronic systemic (oral or injectable) corticosteroids (see exclusion criterion 28)
- Any other immunosuppressive therapy (including methotrexate, cyclosporine, tacrolimus, or maintenance systemic steroid treatment).
- Immunoglobulin or blood products.
- Live, attenuated, or mRNA vaccines if within 2 weeks prior to SV1 only.
- Interferon gamma.
- Other investigational products.
- Marketed biologics.
- Sulfamethoxazole
- Sulfadiazine
- Dapsone
- Propylthiouracil
- Carbimazole
- Methimazole

6.9.1 Rescue Medicine

The following SABAs, as per local SoC, may be used during the study as rescue medication:

1 Salbutamol/albuterol inhalation aerosol, powder, or nebuliser.
2 Terbutaline inhalation aerosol, powder, or nebuliser.

The study site will not supply SABA rescue medication.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention.

Participants will be discontinued from IP in the following situations:

1 Withdrawal of consent to further treatment with study intervention.
2 Lost to follow-up.

3 Adverse event or other safety reasons as judged by the investigator and/or AstraZeneca where continued treatment may put the participant at undue risk.

4 Pregnancy.

5 If it is found that, following randomisation, the participant met ≥ 1 of the exclusion criteria or failed to meet all the inclusion criteria for study participation at or before randomisation, unless the PI and medical monitor agree the participant may continue receiving study intervention.

6 Severe non-compliance to study protocol.

7 Development of uncontrolled and clinically significant thyroid dysfunction as judged by the investigator.

8 Maculopapular rash CTCAE Grades 1, 2, or 3.

9 Any rash or skin reaction that is considered to be an SAE.

10 Generalised rash/skin reaction without an alternative suspect COPD medication (see Section 7.1.1 for details).

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for assessments at end of treatment and during follow-up, including follow-up of any AEs unless consent is withdrawn from further study participation, the participant is lost to follow-up, or the participant is enrolled in another clinical study.

Participants discontinuing study intervention before SV7 should attend the study site for SV7 assessments (as an early treatment discontinuation visit), then attend for SV8 assessments 14 (± 3) days later. In the event a participant is permanently discontinued from further receipt of study intervention, it should be recorded in the IRT/RTMS.

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1 Discontinuation Due to Rash/Skin Reaction

At each visit, participants will be instructed to contact the investigator immediately, if rash or skin reaction has developed. If maculopapular rash CTCAE Grade 1, 2, or 3 has developed, the participant must be permanently discontinued from the study intervention and AstraZeneca medical staff should be informed.

- Grade 1: Macules/papules covering < 10% BSA with or without symptoms (eg, pruritus, burning, tightness).
- Grade 2: Macules/papules covering 10% to 30% BSA, with or without symptoms (eg, pruritus, burning, tightness); limiting Instrumental ADL (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc); rash covering > 30% BSA with or without mild symptoms.
- Grade 3: Macules/papules covering > 30% BSA, with moderate or severe symptoms; limiting Self-care ADL (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

If the participant develops a rash or skin reaction that is not considered a maculopapular rash, but is considered to be an SAE, the participant must be permanently discontinued from the study intervention and AstraZeneca medical staff should be informed.

If the participant develops a generalised rash or skin reaction that is not considered a maculopapular rash or SAE, the participant may continue dosing if the generalised rash/skin reaction occurs following the initiation of another COPD therapy (eg, antibiotics), and in the opinion of the investigator the rash/skin reaction is more likely to have been as a result of this COPD therapy. The suspect COPD therapy must be stopped and the participant must be monitored by the site on a daily basis until the rash/skin reaction has resolved. If, in the opinion of the investigator, the generalised rash/skin reaction does not resolve, worsens, or becomes maculopapular in appearance despite stopping the suspect COPD therapy, the participant must permanently discontinue the study medication. Also, if the participant develops a generalised rash or skin reaction in the absence of alternative suspect COPD medications, the participant must permanently discontinue the study medication. AstraZeneca medical staff should be informed in the event of either occurrence.

For further information and rash/skin reaction evaluation guidance, see Appendix B, B 5.

7.1.2 Temporary Discontinuation

Every attempt should be made to maintain participants on the study intervention during the course of the study. If the study intervention has been interrupted, it should be re-introduced as soon as, in the opinion of the investigator and the participant wishes to resume, the participant is able to re-start study treatment. The treatment period will not be extended to compensate for the temporary discontinuation. Note related to AESI skin reactions (including maculopapular rash): In the occurrence of maculopapular rash CTCAE Grade 1, 2, and 3, or generalised rash/skin reaction without an alternative suspect COPD medication (per Section 7.1.1), or serious rash/skin reaction, study intervention should be permanently discontinued.

At each visit, participants will be instructed to stop the study intervention and contact the investigator immediately if rash or skin reaction has developed. If, after the participant has

been seen by the study doctor or designee, the skin reaction does not meet permanent discontinuation criteria per Section 7.1, the study treatment can be restarted.

In the event that a participant develops symptoms suggestive of COVID-19 infection, the participant should undergo confirmatory rapid screening test for SARS-CoV-2 or PCR testing as soon as possible. Rapid screening test could be either lateral flow test/antigen test or molecular test. If the rapid screening test or PCR test confirms COVID-19 infection, the study intervention should be immediately discontinued on a temporary basis, unless any permanent discontinuation criteria are met (Section 7.1). After discontinuation of study intervention, any appropriate treatment is allowed if conditions presented in Section 6.9 are met.

In the event that a participant develops symptoms suggestive of pneumonia, the participant should undergo confirmatory chest x-ray and appropriate blood testing (eg, hsCRP, complete/full blood count, procalcitonin as deemed appropriate by the investigator) as soon as possible. If chest x-ray confirms the presence of consolidation and clinical markers are consistent with acute infection, the study intervention should be immediately discontinued on a temporary basis, unless any permanent discontinuation criteria are met (Section 7.1). After discontinuation of study intervention, any appropriate treatment is allowed if conditions presented in Section 6.9 are met.

In cases of 'unconfirmed pneumonia', if the participant is not hospitalised and/or does not have a chest x-ray confirming diagnosis of pneumonia, this should generally be considered an infective exacerbation of COPD rather than pneumonia. In this scenario, study intervention can continue. If the investigator still considers this to be pneumonia, then discussion with the AstraZeneca medical monitor would be needed regarding continuation/discontinuation of study intervention.

In case of serious infection, the study intervention should be immediately discontinued on a temporary basis, unless any permanent discontinuation criteria are met (Section 7.1). After discontinuation of study intervention, any appropriate treatment is allowed if conditions presented in Section 6.9 are met.

Study intervention does not need to be stopped for antibiotic treatment of non-serious infection.

If a participant does not receive study intervention for ≥ 28 days continuously, they should be permanently withdrawn from the study intervention.

7.1.3 Restarting After Temporary Discontinuation

Participants who have temporarily discontinued study intervention can resume treatment as soon as, in the opinion of the investigator, the participant is able to re-start study treatment and the participant wishes to resume. No minimum time period is necessary before treatment can

resume, with the exception of participants who temporarily discontinued due to COVID-19, pneumonia or serious infection:

- If the study intervention has been temporarily discontinued due to confirmed COVID19 infection, it may be possible to resume the study intervention at least 7 days after the confirmatory rapid screening test or PCR test if, in the opinion of the investigator, the symptoms related to COVID19 were mild and have resolved.
- If the study intervention has been temporarily discontinued due to confirmed pneumonia or serious infection, it may be possible to resume the study intervention at least 7 days after completion of anti-microbial therapy if, in the opinion of the investigator, the symptoms related to pneumonia or serious infection were not severe and have resolved.

If the participant misses a scheduled visit during temporary discontinuation of study intervention, the missed visit should be recorded as "not done", unless:

- SV5 is missed, in which case it should be performed as soon as possible (eg, when the investigator believes an episode of serious infection, pneumonia or COVID19 has resolved).
- SV7 is missed, in which case it should be performed as soon as possible (eg, when the investigator believes an episode of serious infection, pneumonia or COVID-19 has resolved). The participant should not be re-dosed, but should complete all assessments as per the visit and continue in follow-up (this will ensure data are available at SV7 for the analysis).

7.1.4 Participant Discontinuation at Study End

Enrolment will be stopped after at least 194 first COPDCompEx events have occurred. At this point, all participants enrolled in the study that have not yet completed SV5 should continue in the study to complete 12 weeks of treatment. For these participants SV5 and SV7 should be combined into one visit. Participants who have already completed 12 weeks of treatment when study enrolment is stopped should attend SV7 as soon as possible, continuing treatment until they do. All participants should attend SV8 14 ± 3 days after SV7/EDV.

7.2 Participant Discontinuation/Withdrawal from the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator for behavioural or compliance reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.1.

- At the time of discontinuation from the study, if possible, SV7, as an EDV should be conducted as shown in the SoA (Table 1). See the SoA 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.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw 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, SV7, as an EDV , should be conducted, as shown in the SoA (Table 1). See the SoA 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, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for use of samples, it must be documented in the site study records by the investigator and the investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant 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 study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule. At this time, ascertain whether the participant should or wishes to 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, texts, emails, 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca 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 SoA, 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 SoA.
- Instructions for the collection and handling of human 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.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements. Analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel.
- 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 250 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

The following administrative and general/baseline procedures will be performed:

- Demography
- Medical, COPD, and smoking history
- Assessment of COPD exacerbations
- Physical examination
- Weight and height
- ECG
- Vital signs
- Procedures conducted as part of the participant's routine clinical management (serum chemistry, haematology, urinalysis

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.2.1 COPDCompEx

A COPDCompEx event is a composite endpoint developed to reproduce the treatment effect on COPD exacerbations (52 weeks) in a 12-week study (Vogelmeier et al 2020). COPDCompEx incorporates changes in symptoms, reliever use and PEF obtained from a daily diary, with confirmed exacerbations or study dropouts resulting from a lack of efficacy. The definition of an event is one of the following criteria:

- Moderate or severe exacerbations: episodes leading to one or more of the following: hospitalisation, emergency room visit, an episode of pneumonia, treatment with OCS, corticosteroid injection, or treatment with antibiotics.
- Diary events: defined by threshold and slope criteria using the following diary and home spirometry variables: overall symptom rating, reliever medication use, and change in PEF.
- Study dropouts: withdrawal from a study as a result of a lack of efficacy.

The baseline for COPDCompEx will be estimated during the period between SV2 and SV3. More details on the derivation and analysis of this variable will be given in the SAP.

8.2.2 Chronic Obstructive Pulmonary Disease Exacerbations

8.2.2.1 Assessment of COPD Exacerbation

For the purpose of the protocol, a moderate or severe COPD exacerbation will be defined as a

worsening in the participant's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), may warrant a change in regular medication, and leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.
- Use of antibiotics to treat COPD exacerbation for at least 3 days.
- An inpatient hospitalisation due to COPD (defined as an inpatient admission ≥ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).
- Admission in emergency department or emergency room due to COPD for < 24 hours requiring intensive treatment.
- An episode of pneumonia.
- Results in death.

8.2.2.2 Severity of Chronic Obstructive Pulmonary Disease Exacerbations

A COPD exacerbation will be considered **moderate** if it requires treatment with systemic corticosteroids and/or antibiotics for at least 3 days or resulted in emergency room visit < 24 hours requiring intensive treatment; and does not result in hospitalisation or death.

A COPD exacerbation will be considered **severe** if it results in hospitalisation (defined as an inpatient admission ≥ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system) or death due to COPD.

8.2.2.3 Duration of AECOPD

The start and stop dates of COPD exacerbations will be determined as follows:

The start and stop dates of mild AECOPD will be the onset and resolution of worsened symptoms, respectively.

The start dates of moderate and severe AECOPD will be the earliest of:

- Start date of systemic corticosteroids for AECOPD
- Start date of antibiotics for AECOPD
- Date of hospital admission due to AECOPD

The stop dates of moderate and severe AECOPD will be the latest of:

- End date of systemic corticosteroids for AECOPD
- End date of antibiotics for AECOPD
- Date of hospital discharge due to AECOPD

If less than 7 days have elapsed since the end date of an AECOPD and the start date of a new AECOPD, the second event will be considered a relapse of the prior AECOPD in the statistical analysis.

8.2.3 Spirometry and Peak Expiratory Flow Measurement

At SV1, on-site spirometry will be performed to confirm eligibility for the study using an accredited diagnostic spirometer conforming to ATS/ERS 2019 Spirometry Standards with independent over-reading. Where sites do not have access to such a device, they will be provided with an MIR Spirobank II Smart and android tablet with ZEPHYRx KIOSK mode application. This device and application shall only be used for screening spirometry performed at SV1. Subsequently, a spirometer (MIR Spirobank Smart) will be provided to the participant, paired to a smartphone with the AstraZeneca UNIFY application (also used for the e-Diary and PROs, see Sections 8.2.4 and 8.2.6) at SV2. Spirometry data collection and processing is completed exclusively on the MIR Spirobank Smart device. The MIR Spirobank Smart is regulated as a medical device and is approved for use in all study countries. The UNIFY application will receive spirometry data from the device and acts as an interface to communicate quality of reading and other pertinent information concerning the act of spirometry data collection. The UNIFY application will also send the spirometry data to investigator telemedicine interfaces and study databases.

Full spirometry will be performed at the times indicated in the SoA (Table 1). Data collected will include, but are not limited to, absolute and % predicted (as applicable) PEF, FEV1, FVC, FEV1/FVC, forced mid-expiratory flow ($FEF_{25-75\%}$), and inspiratory capacity.

All spirometry will be performed post-BD, which includes the participant's regular triple or dual (ICS + LABA or LAMA + LABA) therapy. Administration of a SABA should only be necessary if the participant has failed to take their regular inhaled therapy as prescribed in the last 24 hours. In this circumstance, spirometry should be performed at least 15 minutes after the administration of salbutamol 400 mcg, albuterol 360 mcg or terbutaline 500 mcg, or equivalent.

In the event that an adequate quality, maximal effort spirometry effort cannot be obtained at the first attempt during a study visit, a further reattempt is allowed. The participant should be rested for a period of time deemed appropriate by the investigator and have recovered sufficiently for the procedure to be completed safely. This will not be considered rescreening

if undertaken on the same day as the first attempt.

At SV3 and SV5, face-to-face spirometry will be undertaken at the site, followed by virtual spirometry over video link with the participant in a different room from the healthcare professional. Face-to-face spirometry will take the form of supervised, coached measurement by a trained healthcare professional performed in person at the site. Feedback to the participant and session quality assessment will be provided by the healthcare professional in real-time and in adherence with American Thoracic Society 2019 Spirometry criteria (Graham et al 2019). Only measurements obtained by face-to-face spirometry will be utilised for the secondary outcome of post-BD FEV1.

At SV4 and SV7/EDV, virtual spirometry will be performed away from the study site prior to attendance at the site. Virtual Spirometry will take the form of supervised, coached measurement by a trained healthcare professional over a video link (AstraZeneca UNIFY application) with the participant. The healthcare professional will be able to visualise the participant and the spirometry data (including flow-volume loop) over the video link. Feedback to the participant and session quality assessment will be provided by the healthcare professional in real-time and in adherence with American Thoracic Society 2019 Spirometry criteria (Graham et al 2019). Measurements obtained by virtual spirometry will be part of the exploratory analysis only. Face-to-face spirometry, as detailed above, will be performed subsequently once the participant has attended the site.

The same MIR Spirobank Smart spirometer will be used for both forms of spirometry assessment. This is to ensure consistency and comparability of the results and that adequate training and technical setup has occurred. Participants will be asked to bring their spirometer with them to all on-site visits; a “back-up” will be available on-site in case this does not occur.

In addition to the use of face-to-face and virtual spirometry data collection, the patient will use the MIR Spirobank Smart and UNIFY application to undertake twice daily, unsupervised PEF-only measurements, which will form part of the COPD CompEx assessment. The patient will be suitably trained on how to use the MIR Spirobank Smart and UNIFY application to record PEF measurements.

8.2.4 Participant-Reported Outcomes

The following assessments will be performed to evaluate respiratory symptoms at the times indicated in the SoA (Table 1). Participants should complete on-site PRO assessments before all other scheduled assessments in a quiet area. The appointed site personnel should also stress that the information is confidential. Therefore, if the participant has any medical problems, he or she should discuss them with the doctor or study nurse separately from the PRO assessments.

All PROs will be completed on the e-Diary. The participant will be asked to bring the device

with the e-Diary on with them to all on-site visits.

- Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT)

The EXACT is a 14-item ePRO instrument developed to assess the frequency, severity and duration of COPD exacerbations (Jones et al 2011; Leidy et al 2011). The instrument was developed for daily, at home, administration using a handheld electronic device. Respondents are instructed to complete the diary each evening just prior to bedtime and to answer the questions while considering their experiences "today". The daily EXACT total score has a range of 0 to 100 with higher scores indicative of greater severity. Total score changes are used to identify the onset and recovery from an EXACT defined exacerbation event. In identifying event onset and recovery, the EXACT can provide information on event frequency and duration as well as event severity.

The EXACT will be performed at on-site visits using the e-Diary. The EXACT questionnaire is presented in Appendix G.

- Breathlessness, Cough and Sputum Scale (BCSS)

The BCSS is a 3-item questionnaire rating breathlessness, sputum, and cough on a 5-point Likert scale from 0 (no symptoms) to 4 (severe symptoms) (Leidy et al 2003). Item scores can be reported as domains scores and are summed to yield a total score. The BCSS will be captured each evening via the e-Diary over the period indicated in the SoA (Table 1). The recall period for the BCSS is "today".

- Cough Visual Analogue Scale (Cough VAS)

Participants will be asked to complete a cough severity VAS (100-point linear scale marked with a horizontal or vertical line by the participant, with 0 representing "no cough" and 100 representing "worst cough") measuring subjective assessment by the participant of the prior 24 hours for severity of cough symptoms (Smith et al 2006). The Cough VAS will be completed each morning in the e-Diary over the period indicated in the SoA (Table 1). The Cough VAS is presented in Appendix I.

8.2.5 COPD Assessment Test

The CAT is designed to measure how COPD impacts on a participant's daily life and how this might change over time (Jones et al 2009). It consists of 8 questions that ask the participant to rate items relating to symptoms and impact on quality of life (such as normal activity and sleep). Each question is performed on a 5-point Likert scale from 0 (no symptoms/no impact) to 5 (severe symptoms/impact). The CAT will be completed by participants at on-site visits using the e-Diary as indicated in the SoA (Table 1). The CAT is presented in Appendix H.

8.2.6 E-Diary

The e-Diary will be provided to participants at Visit SV2, at which point they will receive

training on its use.

Participants will record information in their e-Diary twice a day.

The participant will be asked to bring the e-Diary on with them to all on-site visits.

The following parameters will be reported by participants according to the SoA (Table 1):

- COPDCompEx parameters
- BCSS
- OCS use, antibiotic use, and hospitalisation
- Cough VAS
- Study intervention administration at home
- EXACT
- CAT
- Self-photos of skin affected with rash/skin reaction

Participants must demonstrate a compliance of at least 70% during the 14 days preceding SV3 to be eligible for randomisation (defined as completing the daily diary for any 10 mornings, any 10 evenings, and performing PEF for any 10 morning and any 10 evenings).

During the study treatment period, daily eDiary compliance is critical for overall symptom rating, reliever medication use, and change in PEF. The investigator/authorised delegate should check the participant's adherence to the daily eDiary at each visit during the study and at any time during the study. If it drops below 80% to 85%, sites should take steps to ask the participant about the reason and to encourage the participant to regularly complete the eDiary.

See Appendix I for the BCSS and Cough VAS assessments to be completed.

If technical or other issues prohibit completion, an appropriate back-up option may be considered with prior approval from AstraZeneca.

8.2.7 Optional Computed Tomography Scan

The purpose of the optional CT scan is to characterise and assess the severity of COPD at baseline by, among other approaches, evaluation of the distribution of emphysema and visualisation of small airways disease, mucous plugging, and/or bronchiectasis. It is anticipated that a more detailed analysis of responders to treatment will be done on the basis of pre-existing emphysema severity and the presence of mucous plugging in particular. This may guide the inclusion of patients in the subsequent development program and will also be used to explore the association with the other biomarkers of disease progression from both

blood and sputum biomarker sampling. To support this analysis it is preferred that the majority of participants within the study should have a CT scan undertaken or results of a historical CT scan available, where feasible.

Where an inspiratory and expiratory chest CT scan has been performed within 6 months of informed consent and can be obtained and is adequate for quantitative assessment, it can serve as the baseline scan. Otherwise, an optional CT scan can be performed, per Table 1, to serve as the baseline scan. The high resolution CT could be performed as soon as main eligibility criteria are confirmed at SV1 which include blood test results, up to randomisation. If a CT scan is performed during the study, the local CT scan report must be obtained before randomisation.

In order to avoid unnecessary radiation exposure, a CT scan to serve as the baseline scan should only be performed if all of the following criteria are met:

- The participant does not meet Exclusion Criterion 7(g) (given available clinical, radiological and other data),
- The participant has not had an inspiratory and/or expiratory chest CT scan within 6 months of informed consent, which can be obtained and is adequate for quantitative assessment, and
- The participant is believed to be eligible, at the time, according to all inclusion and exclusion criteria.

Quantitative assessment for the extent of emphysema of the baseline scan will be performed, using procedures described in the vendor manual provided to sites.

All CT scans performed (or used) for the purposes of this study should be locally reviewed by a suitably qualified radiologist for clinical findings outside of emphysema and morphometric assessment, to ensure any incidental clinically important findings are identified and referred/treated appropriately (eg, suspected cancer) (this local review may be performed remotely in accordance with local practices). If a participant had recent lung imaging either in the study or before the screening that requires immediate diagnostic investigation or follow-up, they must not be randomised. If initial repeat surveillance imaging has been undertaken, and the abnormality is considered low risk of malignancy, the participant may be eligible for enrolment following confirmation with the AstraZeneca medical monitor. (Exclusion Criterion 7(g)).

New (optional) CT scans must be performed in a standardised way:

- All new CT scans should be performed post-BD which includes the participant's regular triple or dual (ICS + LABA or LAMA + LABA) therapy. When these are undertaken at the same visit as spirometry, the CT should be performed after these assessments.
- Both full inspiration and end expiration sequences should be obtained.

A radiology manual, as well as further training by the imaging vendor, will describe both the process of obtaining new scans and how to submit scans (historical and new) to the imaging vendor. An optimised CT protocol will also be provided to the sites that includes all required scan parameters. Full compliance with the imaging vendor protocol is preferred, but where this is not possible, an adapted clinical protocol which is adherent to the above principles may be acceptable after discussion with AstraZeneca.

Any clinical findings from historical CT should be recorded on the specific imaging eCRF page for SV3. Any findings based on the local assessment of a new CT scan performed during screening must be recorded in the corresponding eCRF section.

All CT images submitted to the imaging vendor (VIDA, Iowa, US) must first be de-identified at the site to remove any participant identifiers. No clinical interpretation of the CT scans will be performed by the central imaging vendor.

8.2.8 Cough Substudy

The assessments described in Section 8.2.8.1 are only applicable to participants of the cough substudy.

8.2.8.1 VitaloJAK® Cough Monitor Device

Twenty-four-hour ambulatory monitoring of coughing will be performed at timepoints as specified in the SoA (Table 1). The assessment of 24-hour coughs per hour (ie, average hourly cough frequency based on 24-hour sound recordings) will be evaluated using the VitaloJAK® Ambulatory Cough Monitor (ACM) (Vitalograph, Buckinghamshire, UK), which has been implemented successfully in clinical studies of potential cough therapies. Participants will be provided with the device and appropriate training for its use. The participants will be able to manually mute the recordings. Data from the device will be filtered for voice frequencies, and speech will not be analysed. If the first recording is successful but the Week 12 recordings are not usable, the Week 12 assessment can be repeated as soon as possible but no later than Week 18. If the first recording at start of treatment is unsuccessful, the Week 12 recording can be omitted. The participants will be asked to return the device to site after completion of recording as soon as feasible. At some sites, the participants will also have the option of having the device collected, eg, by courier. This data will not be used for any safety assessments. The VitaloJAK® Cough Monitor is regulated as a medical device and has import

approval in each study region where the cough substudy will be performed.

The VitaloJAK® Cough Monitor will be fitted and worn by the participants for approximately 24 hours after the visits detailed in the SoA (Table 1). Set up of the cough monitors should be performed as the final assessment at each visit. The sites will receive training to ensure the ACM is correctly fitted and activated by site staff, and the site staff will be given instructions to provide to the participants on how the ACM should be worn during the 24-hour period, to ensure data are recorded correctly. Advice includes avoiding showers/bathing and any activity that will cause heavy perspiration whilst wearing the cough monitor, as the cough monitor must not come into contact with water. The data digitally recorded on the ACM will be sent to Vitalograph who will undertake cough counting for all participants using a standardised process. Details on the process to follow will be provided to the sites as part of the ACM training. Detailed procedures for set up of device, recording and analysing objective cough data will be described in a separate manual provided to each site. Details regarding assessment of the quality of objective cough monitoring undertaken by the vendor will also be detailed in the manual.

8.2.9 Q-SAW Substudy

Participants from selected sites in selected countries, who provide written informed consent, will be eligible to participate in the Q-SAW substudy. Not all participants that provide consent will be interviewed.

Participants may be invited to 2 semi-structured interviews: an initial interview and a second interview up to 6 weeks later. Each interview will take approximately 30 minutes and will be conducted over video call or telephone call. A topic list and interview guide with example questions will be used as a framework for the interviews (Appendix L 3).

This substudy will be conducted by an external vendor, GPRI (Groningen, Netherlands).

Results of this substudy will be reported separately from the CSR.

Further details of the Q-SAW substudy are described in Appendix L.

8.2.10 SPFQ Substudy

Participants at selected sites will be eligible to complete the SPFQ, which will give participants the opportunity to provide feedback on their clinical study experience. Informed consent will be given via the UNIFY platform immediately prior to completing the questionnaire.

Participants will be asked to complete the questionnaire at the beginning, middle and end of the study in electronic format via the UNIFY platform as specified in the SoA (Table 1).

Results of this substudy will be reported separately from the CSR.

Further details of the SPFQ Substudy and a copy of the SPFQ are shown in Appendix M.

8.2.11 Patient Experience Interview Substudy

A subsample of participants from selected sites in selected countries will be invited to take part in a semi-structured interview. The interview will take approximately 60 minutes and will be conducted video or telephone call via Zoom. The timepoints of the interviews will be stratified over the study duration, starting after at least 2 study visits. A topic list and interview guide will be used as a framework for the interviews (Appendix N 2).

This substudy will be conducted by an external vendor, GPRI (Groningen, Netherlands).

Results of this substudy will be reported separately from the CSR.

Further details of the Patient Experience Interview Substudy are described in Appendix N.

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.3.1 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 skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.3.2 Vital Signs

Vital signs (supine BP [average of 3 measurements], respiratory rate, pulse rate, and body temperature) will be performed in-clinic at timelines as specified in the SoA (Table 1).

Vital sign assessments are to be collected using equipment supplied by the investigator.

At Visits SV3 and SV5, the vital signs BP measurements can be used for the pre-dose supine measurements for the orthostatic test, if taken after being supine for at least 10 minutes and as long as the standing BP measurements are taken after these supine measurements at the time intervals described below for the orthostatic blood pressure measurement.

The measurements should be done before any blood sampling. The measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

Orthostatic Blood Pressure Measurements and Follow-up of Confirmed Orthostatic Hypotension

Orthostatic BP measurements will be obtained using a standard sphygmomanometer after scheduled supine measurements (1 and 3 minutes after the participant stands) and prior to any required blood draw:

- At SV3 (baseline; Day 1), orthostatic BP should be measured pre-dose and 1 to 2 hours post dose.
- At SV5 (Week 12), orthostatic BP should be measured pre-dose.

To minimise chances of orthostatic hypotension related to volume depletion, participants should be well hydrated when they come to the clinic for study visits. Supine BP measures will be collected after participants have been lying down for at least 10 minutes. To ensure that a stable supine BP is obtained, at least 2 systolic and 2 diastolic BP measurements will be obtained. If the replicate measurements differ by no more than 10 mmHg and 5 mmHg, respectively, the supine BP will be considered stable. The mean value of each replicate (mean systolic and mean diastolic value) will represent the baseline BP for that visit. After stable BP is achieved, the participant will stand, and BP measurements will be taken at 1 and 3 minutes after the participant stands. If the BP measurements do not meet the criteria for orthostatic hypotension, no additional measurement is needed. If the BP measurement meets the criteria shown in Table 5, investigators will repeat the supine and standing measurements up to 2 additional times. The exception is for participants with orthostatic hypotension symptoms: in this situation, the orthostatic hypotension AE should be reported based on a single orthostatic test sequence.

When evaluating orthostatic vital signs, any symptoms of dizziness or light headedness should be recorded on the AE page in the eCRF. At Visit SV3, if orthostatic hypotension is confirmed pre-dose and post-dose, the orthostatic hypotension AE should be reported twice (pre-dose and post-dose). The same applies to symptoms related to the measurement of orthostatic vitals: if present pre-dose and post-dose, it should also be reported as an AE twice (pre-dose and post-dose).

Table 5 Orthostatic Blood Pressure Criteria and Management

Decrease in BP indicative of orthostatic hypotension	Actions
≥ 20 mmHg systolic or ≥ 10 mmHg diastolic	Repeat the BP measurements (supine and standing) up to 2 additional times, unless orthostatic hypotension is present in association with symptoms related to the measurement of orthostatic vitals: in such a case the test does not need to be repeated and the orthostatic hypotension AE and symptoms related to the measurement of orthostatic vitals AE should be reported based on a single sequence. If either the 1-minute or 3-minute standing BP meets the orthostatic (postural) hypotension criteria, then the sequence is considered indicative of orthostatic hypotension. If 2 of 2 or 2 of 3 sequences are positive, then orthostatic hypotension is confirmed, and an AE of orthostatic hypotension will be reported.

AE = adverse event; BP = blood pressure.

For participants with orthostatic hypotension, individualised treatment should be prescribed at the investigator's discretion following local guidelines, including pharmacological (eg, down titration of nitrates) or non-pharmacological (eg, hydration) treatments.

8.3.3 Electrocardiograms

12-lead ECG will be performed in-clinic at timepoints as specified in the SoA (Table 1).

Single 12-lead ECG (standard ECG with a paper speed of 25 to 50 mm/second covering at least 6 sequential beats) will be obtained after the participant has been resting in a supine position for at least 5 minutes, at the visits outlined in the SoA (Table 1). An ECG machine that automatically calculates the heart rate and RR interval and measures PR, QRS, QT, and QTcF (Fridericia) intervals will be used. Interpretation of the clinical safety ECG findings will be reviewed and confirmed by the investigator and recorded in the eCRF.

Electrocardiogram assessments are to be collected using equipment supplied by the investigator.

8.3.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken in-clinic or at a designated phlebotomy service location at the visits indicated in the SoA (Table 1).

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study. Clinical laboratory safety tests will be performed at the central laboratory, except for tests completed using urine dipstick tests, which will be done

locally (see Table 6 for details of these tests). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 hours).

Additional safety samples, including ANCA 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.

The laboratory variables to be measured are presented in Table 6.

Table 6 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
Urinalysis (dipstick)	S/P-Alanine transaminase (ALT)
Leukocytes	S/P-Albumin
Nitrite	S/P-Potassium
Urobilinogen	S/P-Calcium, total
Protein	S/P-Sodium
Blood	S/P-Creatine kinase (CK)
Ketone	**Thyroid tests**
Bilirubin	Free T4 and total T4
Glucose	T3
Other	Thyroid stimulating hormone (TSH)
FSH (screening only, if needed to confirm post-menopausal status in female participants aged < 50 years only)	**Coagulation parameters (screening only)**
ANCA (optional if rash AE occurs, at the discretion of investigator)	Prothrombin time (PT)
Viral serology (screening only):	Activated partial thromboplastin time (aPTT)
Hepatitis B	International normalised ratio (INR)
Hepatitis C	Fibrinogen
HIV-1	

- **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.

8.3.5 SARS-CoV-2 Screening

A SARS-CoV-2 (COVID-19) screening test can be performed at the time of study visits if required by local clinical guidelines for the safety of site staff and other site attendees but otherwise is not mandated in the study.

8.4 AEs, SAEs, and Other Safety Reporting

The PI 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.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

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

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Maximum CTCAE grade for maculopapular rash and non-maculopapular rash
- Whether the AE is serious or not
- Investigator causality rating against the IMP (yes or no)
- Action taken with regard to IMP
- Whether the event is a serious infection including pneumonia or skin reaction including maculopapular rash
- AE caused participant's withdrawal from the 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 description
- AE is serious due to
- 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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of first dose of study intervention throughout the treatment and the follow-up periods (SV8; Table 1). The only exception is related to the pre-dose orthostatic test at Visit SV3: if orthostatic hypotension is confirmed, it should be reported as an AE, and symptoms related to the measurement of orthostatic vital signs if present should also be reported as an AE.

Serious adverse events 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 IMP that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to AstraZeneca.

Participants should be reminded at each visit to contact the investigator immediately, if rash or skin reaction has developed.

8.4.2 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, 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.

8.4.3 Causality Collection

The investigator should assess causal relationship between IMP 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 IMP?'

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.

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated measurements should only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria
- are the reason for discontinuation of the IMP
- are clinically relevant as judged by the investigator (which may include but not be limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or 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. 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).

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.

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

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms 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 the previous visit/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.

8.4.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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.

8.4.7 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of COPD. Events which are unequivocally due to disease under study should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP.

8.4.8 Reporting of SAEs

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately 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 within one calendar day, ie, immediately 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 eCRF, an automated email alert is sent to the designated AstraZeneca representative.

If the eCRF is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the eCRF is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca eCRF when access resumes.

8.4.9 Adverse Events of Special Interest

The following events are defined as AESI for mitiperstat (AZD4831) in this study:

Skin reactions, including maculopapular rash

To ensure that data are collected systematically, any skin reaction will be recorded on a special eCRF page. All skin reactions should be recorded in the eCRF as an AE or SAE. If the rash is considered maculopapular, it will be evaluated using CTCAE Grades 1 to 3 for maculopapular rash; if not considered maculopapular, severity will be captured as mild/moderate/severe, along with data element components generally used for CTCAE grading of other skin reactions, given that CTCAE grading is specific to the particular type of skin lesion. For all rashes, various aspects of the rash will be documented, including start/end date, morphology of lesions (maculopapular vs other morphologies), BSA impacted, anatomical site(s), symptoms, effect on participant (including ADL impacted), concomitant medications, medication administered, and specific rash diagnosis, if available. Photos (overview and detailed) should be taken. Please refer to Appendix B, B 5 for further guidance in rash assessment and reporting.

At all visits, participants will be instructed to contact the investigator immediately if rash or skin reaction has developed at any timepoint during the study. Participants will be recommended to make an acceptable quality self-photo of skin affected with rash/skin reaction.

Participants who develop skin reactions, including rash, will be asked to return to the clinic for an additional visit that will include a full physical examination and blood samples for safety, hsCRP, and PK. If a participant is discontinued from investigational product and proceeds to the EDV (SV7/EDV; see Table 1), an exploratory biomarker sample and blood and urine samples for exploratory metabolite analysis will also be collected. It is suggested to start treatment for maculopapular rash, per local standard treatment guidelines (which may include, but not be limited to, a topical steroid and/or oral antihistamine). The treatment should be individualised per participant and based on PI discretion. Upon PI discretion, a clinical dermatologist can be consulted, and a skin biopsy considered. The participant can be provided with a treatment for the skin rash, according to clinical management standard. Blood samples should be drawn prior to treatment, if possible, and without delaying treatment.

Serious infections, including pneumonia

Local laboratory testing for microorganisms per local guidelines is requested for serious infections (those that meet SAE criteria) and results documented. Any imaging reports and scans should be uploaded to the Medidata imaging portal and included in source documents.

8.4.10 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.

8.4.10.1 Maternal Exposure

Females of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the study intervention should be discontinued immediately, and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/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 anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but **no later than 24 hours** after 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 pregnancies associated with SAEs (see Section 8.4.8) 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 and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.4.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm from Day 1 until the end of relevant systemic exposure in the male participant, plus a further 105 day period.

In case of pregnancy in the partner of a male participant, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should, if possible, be obtained and documented.

8.4.11 Medication Error, Drug Abuse, and Drug Misuse

8.4.11.1 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 8.4.8) and **within 30 days** for all other events.

8.4.11.2 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.

8.4.11.3 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.

8.4.11.4 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.

8.4.12 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/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 8.4.8) and **within 30 days** for all other overdoses.

8.4.13 Medical Device Deficiencies

In this study any deficiency observed with a third-party medical device will be reported directly to the third-party manufacturer by the study site staff according to the contact details in the device Instructions For Use.

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.

The manufacturer's medical device complaint report will be used to collect the deficiency.

8.5 Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of mitiperstat (AZD4831) as specified in the SoA (Table 1). Pharmacokinetic samples will be collected pre-dose; thus, participants should be reminded not to take their study medication at home on the day of their clinic visit as they will receive study medication in clinic on these days.
- In a subset of approximately 20% of participants, 2 additional (post-dose) samples will be taken at SV5. Once approximately 20% of participants have been tested, no further participants need this additional post-dose sampling.
- For participants who are discontinued from investigational product due to rash, a PK sample should be collected at the discontinuation visit.
- Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.

- The timing of sampling may be altered during 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.
- Plasma samples will be used to analyse the PK of mitiperstat (AZD4831). Samples collected for analyses of mitiperstat (AZD4831) plasma 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.
- For storage, re-use, and destruction of samples for PK see Appendix C.
- Pharmacokinetics 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.
- Only samples from participants on active treatment will be analysed (Section 6.3), unless there is a need to confirm that correct treatment has been given to study participants.
- 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.

8.5.1 Collection of Samples for Pharmacokinetics

Blood samples will be collected for measurement of mitiperstat (AZD4831) as specified in the SoA (Table 1).

Blood and urine samples will be collected for exploratory metabolite analysis as specified in the SoA (Table 1).

8.5.2 Determination of Drug Concentration

Samples for determination of drug concentration in plasma 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.

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.

8.6 Pharmacodynamics

8.6.1 Collection of Samples for Pharmacodynamics

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

Blood and sputum samples will be collected for PD assessments as specified in the SoA (Table 1).

Pharmacodynamic blood samples to assess:

- Systemic target engagement: blood samples will be taken to assess MPO activity and concentration in a subsample of approximately 60 participants in selected countries.

Pharmacodynamic sputum samples to assess:

- Target engagement: sputum samples will be taken to assess MPO activity and concentration in sputum supernatant.

For storage, re-use and destruction of samples for PD see Appendix C.

8.7 Optional Genomics Initiative Sample

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

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study (see SoA; Section 1.3). Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices of this protocol or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Biomarkers

8.8.1 Mandatory Biomarker Sample Collection

- Samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA (Table 1).
- Samples will be tested for biomarkers related to cardiovascular comorbidities, neutrophils, lung tissue destruction, the development of skin reactions, and COPD disease

activity to evaluate their association with the observed clinical responses to mitiperstat (AZD4831) compared with placebo.

Blood samples to assess:

- Systemic biomarkers of cardiovascular comorbidities: NT-proBNP, hsCRP, IL-6, and plasma fibrinogen. *
- Putative biomarkers of lung tissue destruction and COPD disease progression. *
- Putative circulating markers of airway MPO as assessed by proteomics. *
- Gene expression as assessed by transcriptomic analysis of mRNA. *

Sputum samples to assess:

- MPO concentration and activity.
- Other markers of inflammation and neutrophil activation. *
- Putative biomarkers of lung tissue destruction and COPD disease progression. *
- Differential cell counts (at SV3 only, where local equipment for analysis is available).*

Nasal mucosal lining fluid samples to assess:

- MPO concentration and markers of lung tissue destruction. *

* will not be delivered prior to database lock and will not be part of the CSR.

For participants who discontinue investigational product due to rash or skin reaction, blood and urine will be collected at the EDV for exploratory biomarker analysis in blood and analysis of mitiperstat (AZD4831) metabolites in urine and plasma. Samples will be collected, handled, labelled, stored, and shipped as detailed in the Laboratory Manual. For storage, re-use and destruction of exploratory samples, see Appendix C.

8.8.2 Optional Cell-free DNA Analysis Sample Collection

Two blood samples for cell-free DNA analysis (see SoA; Table 1) will be collected from participants who have consented to participate in the genomic 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.

8.9 Medical Resource Utilisation and Health Economics

Health economics/Medical resource utilisation and health economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

Null hypothesis that there is no difference in the time to first COPDCompEx event in mitiperstat (AZD4831) 5 mg QD vs placebo with an alternative hypothesis that there is a difference in the time to first COPDCompEx event. As a single logrank test, adjustment for multiple testing will not be required.

9.2 Sample Size Determination

The study is powered using COPDCompEx, a composite endpoint used to predict treatment effect on moderate and severe exacerbations of COPD (see Section 8.2.1).

The time to first COPDCompEx event will be compared between mitiperstat (AZD4831) 5 mg QD vs placebo arms using a logrank test. A total of 194 first COPDCompEx events (estimated to require 203 participants per arm) will provide 80% power at the two-sided 10% level of statistical significance to detect a hazard ratio of 0.70 in the mitiperstat (AZD4831) 5 mg QD arm based on a 24-week first COPDCompEx event risk of 55% assumed in the placebo arm (constant over the course of the study).

A screen failure rate of 40% is assumed, therefore approximately 677 participants will be screened to achieve randomisation of 406 participants.

For all other secondary or exploratory endpoints, no formal sample size calculation was performed. Further information is available in the SAP.

9.3 Populations for Analyses

The following populations are defined:

Table 7 Populations for Analysis

Population/Analysis set	Description
Full Analysis Set (FAS)	Will include all randomised participants who received at least 1 dose of study intervention. Participants will be analysed according to planned treatment. Efficacy analyses will be based on the FAS.
Safety Analysis Set (SAF)	Will include all participants who received at least 1 dose of study intervention. Participants will be analysed according to actual treatment. Safety analyses will be based on the SAF.
Per Protocol Set (PP)	Will include all participants in the FAS who have no important protocol deviations thought to affect the analysis of COPDCompEx and FEV1 data.
PK Analysis Set	Will include all participants who received mitiperstat (AZD4831) and who have evaluable PK data for mitiperstat (AZD4831), with no important protocol deviations thought to impact on the analysis of the PK data.
Randomised Set	Will include all participants who have been randomised.
Cough subset	Will include the subset of FAS who consented to the cough substudy.

Participants will be analysed according to their randomised study intervention arm.

9.4 Statistical Analysis

9.4.1 General Considerations

The statistical methodology below describes the high-level statistical analysis as it is foreseen when the study is being planned.

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. Continuous data will be summarised using descriptive statistics (number of observations, mean, SD, median, 25th and 75th percentiles [where appropriate], minimum and maximum). In the case of log-transformed data, the geometric mean, CV% of geometric mean, median, minimum, and maximum will be presented. Frequencies and percentages will be used to summarise categorical data. Only the minimum, median, and maximum will be presented for time parameters such as t_{max}.

Deviations from the protocol will be assessed as “important” or “not-important” by **blinded members of the study team**.

Deviations will be defined before database hard lock and unblinding. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria

- Participants who developed withdrawal criteria during the study but were not withdrawn
- Wrong study intervention or incorrect dose administered
- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint

A BDRM will be held before database hard lock and unblinding. The reasons for excluding participants or data from the study will be defined in the SAP and documented in the BDRM report.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

The primary endpoint to evaluate the clinical efficacy of mitiperstat (AZD4831) 5 mg compared with placebo is time to first COPDCompEx event. After at least 194 first COPDCompEx events have occurred, enrolment will be stopped and when the last participant completes 12 weeks of treatment, the study will stop (see Section 7.1.4). A logrank test and Cox's proportional hazards model will be used to analyse the time to first COPDCompEx event data. Survival probabilities will be presented as survival curves estimated using the Kaplan-Meier method. A two-sided logrank test *P*-value ≤ 0.10 is required to provide evidence of efficacy.

The primary estimand strategy for intercurrent events will be while on treatment and the supportive estimand strategy will be treatment policy (see Table 3). Model assumptions will be checked and mitigations for possible non-proportionality will be described in the SAP.

9.4.2.2 Secondary Endpoints

A similar approach to that described for the primary efficacy endpoint will be applied to the secondary endpoint: time to first exacerbation.

In order to ensure that the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates ≤ 7 days apart will be considered the same event and assigned the maximum severity between the two. Time during an exacerbation or in the 7 days following an exacerbation will not be included in the calculation of time at risk. However, the start day of a COPD exacerbation will not be excluded from the time at risk.

Any COPD exacerbation that occurs within 7 days of the last dose of systemic corticosteroids (oral, intramuscular, intravenous) or antibiotics or the last day of hospitalisation or emergency room visit for a prior COPD exacerbation will be combined and counted as a single exacerbation event and as the maximum severity between the individual events. Further details on combining exacerbation events will be provided in the SAP. Consistent criteria will be applied to all exacerbation endpoints.

Plasma concentrations will be summarised by timepoint in all participants. Pharmacokinetic data for those participants with additional PK sampling at Visit SV5 will be used to derive plasma PK parameters such as C_{max} and t_{max}.

9.4.2.3 Tertiary/Exploratory Endpoints

Details for the analyses of exploratory efficacy endpoints will be included in the SAP.

9.4.3 Safety

Adverse Events

Adverse events will be coded using the most recent version of MedDRA that will have been released for execution at AstraZeneca. Adverse events will be presented for each treatment group by 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 overview of AEs will be presented for each treatment group the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of IP.

Separate AE tables will be provided taking into consideration seriousness, death, and events leading to discontinuation of IMP. An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency of > x%, ≥ x%) 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 participants information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IMP. An AE listing for the SAF will cover details for each individual AE. AESIs related to skin reactions, including maculopapular rash, and infection, including pneumonia, will be presented. Full details of AE analyses will be provided in the SAP.

Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, min, Q1, median, Q3, and max. For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline. Details of vital sign analyses will be provided in the SAP.

Laboratory Parameters

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum. For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline. A frequency table

presents the number of participants reporting at least one abnormality in selected laboratory parameters. Details of laboratory analyses will be provided in the SAP.

Electrocardiogram

Electrocardiogram parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, minimum, Q1, median, Q3, and maximum. For each scheduled post-baseline assessment, descriptive statistics for all ECG parameters will be presented for observed values and change from baseline. Supportive ECG listings will cover observed values for each individual participant. Details of ECG analyses will be provided in the SAP.

9.5 Interim Analysis

An administrative IA will be conducted after 136 (70% of the required 194) first COPDCompEx events have occurred. It will allow an early assessment of efficacy for mitiperstat (AZD4831), according to the decision framework (Frewer et al 2016). No formal statistical test will be conducted. The IA assessment will be used to guide internal (AstraZeneca) decision-making regarding further development of the mitiperstat (AZD4831) programme. As a result, no alpha will be spent at the IA. A URC will be set up to review data from this administrative IA on the primary efficacy endpoint. (see Appendix A 5 for further details).

The URC charter will describe the planned administrative IA in greater detail.

9.6 Data Review Committee

The DRC members will be notified on an ongoing basis of all skin reaction and pneumonia events and can call a meeting at any time to discuss the event frequency. Although not part of the IA, the DRC will conduct an evaluation of safety at the time of the administrative IA, to allow efficacy IA outcome data to be considered should it be required. For details on the DRC for this study, see 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 as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, Investigator's Brochure, 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 revised 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 (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an 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.
- AstraZeneca 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. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and AstraZeneca 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the Investigator's Brochure and other relevant documents 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 AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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 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 or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection 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.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be 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 AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca 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 AstraZeneca 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

AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

A 5 Committees Structure

- A URC consisting only of AstraZeneca personnel will require unblinding and will be independent from the study team. The URC will ensure that the IA is performed in a way that maintains the integrity of the study and in accordance with the IA unblinding plan. The URC will communicate to the study team as specified in the URC charter.
- A DRC consisting of AstraZeneca personnel, an external dermatologist, and an external pulmonologist will be set up for periodic safety monitoring, with a focus on skin reactions and pneumonia. The AstraZeneca personnel in the DRC will be independent from the study team. At the time of the IA, the DRC will assess the safety profile (ie, all AE data) of mitiperstat (AZD4831) and will have access to IA outcome data, if required. Additional details will be contained in the DRC Charter.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.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 CRESCENDO study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca 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, including definition of study-critical data items and processes (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 included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan(s).
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) 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 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global Retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

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 the source data verification plan.

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 first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca 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, AstraZeneca's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

Reasons for the early termination of the study by AstraZeneca may include but are not limited to:

- The incidence, frequency, duration or severity of AEs in this or other studies exposing participants to undue harm.
- Participant enrolment is unsatisfactory.
- Non-compliance that might significantly jeopardise the validity or integrity of the study.
- AstraZeneca decision to terminate development of the investigational product for this indication.
- Unjustifiable risk resultant from the risk-benefit assessment conducted at the IA.

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) 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.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

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 AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre 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 patient 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 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, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly 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 **SAEs**. 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-SAE**. 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 medicinal 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

Outpatient treatment in an emergency room is not in itself an SAE, 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 intravenous 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 an 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 an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing 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 rechallenge.
- 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 AstraZeneca study intervention 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 the 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 fridge 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 regards 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

B 5 Guide to Skin Reaction Assessment

This Appendix describes the process to be followed to appropriately identify, assess, and report cases of skin reactions. Skin reactions, including maculopapular rash, will be considered AESIs in this study. To ensure that data are collected systematically, any skin reaction will be recorded on a special eCRF page. All skin reactions should be recorded and reported as AEs or SAEs.

If the rash is considered maculopapular, it will be evaluated using CTCAE Grades 1 to 3 for maculopapular rash; if not considered maculopapular, severity will be captured as mild/moderate/severe, along with data element components generally used for CTCAE grading of other skin reactions, given that CTCAE grading is specific to the particular type of skin lesion. For all rashes, various aspects of the rash will be documented, including start/end date, morphology of lesions (maculopapular vs other morphologies), BSA impacted, anatomical site(s), symptoms, effect on participant (including ADL impacted), concomitant medications, medication administered, and specific rash diagnosis, if available.

If maculopapular rash Grade 1, 2, or 3 has developed, participant must be permanently discontinued from IP, and AstraZeneca medical staff should be informed.

If the participant develops a rash or skin reaction that is not considered a maculopapular rash, but is considered to be an SAE, the participant must be permanently discontinued from the study intervention and AstraZeneca medical staff should be informed.

If the participant develops a generalised rash or skin reaction that is not considered a maculopapular rash or SAE, the participant may continue dosing if the generalised rash/skin reaction occurs following the initiation of another COPD therapy (eg, antibiotics), and in the opinion of the investigator the rash/skin reaction is more likely to have been as a result of this COPD therapy. The suspect COPD therapy must be stopped and the participant must be monitored by the site on a daily basis until the rash/skin reaction has resolved. If, in the opinion of the investigator, the generalised rash/skin reaction does not resolve, worsens, or becomes maculopapular in appearance despite stopping the suspect COPD therapy, the participant must permanently discontinue the study medication. Also, if the participant develops a generalised rash or skin reaction in the absence of alternative suspect COPD medications, the participant must permanently discontinue the study medication. AstraZeneca

medical staff should be informed in the event of either occurrence.

At all visits, participants will be instructed to contact the investigator immediately if rash has developed at any timepoint during the study. Participants will be recommended to make an acceptable quality self-photo of skin affected with rash using the provisioned handheld device.

Participants who develop skin reactions, including rash, will be asked to return to the clinic for an additional visit that will include a full physical examination and blood samples for safety, hsCRP, and PK. If a participant is discontinued from investigational product and proceeds to the EDV (SV7/EDV; see Table 1), an exploratory biomarker sample and blood and urine samples for exploratory metabolite analysis will also be collected. It is suggested to start treatment for maculopapular rash, per local standard treatment guidelines (which may include but not be limited to a topical steroid and/or oral antihistamine).

The treatment should be individualised per participant and based on PI discretion. Upon PI discretion, a clinical dermatologist can be consulted, and a skin biopsy considered. The participant can be provided with a treatment for the skin rash, according to clinical management standard. Blood samples should be drawn prior to treatment, if possible, and without delaying treatment.

The investigator should make quality photo(s) of the participant's skin affected with rash using the Medidata imaging application, that will allow the evaluation of rash according to the guidance given in this section.

The Common Terminology Criteria for AEs is a descriptive terminology that can be used for AE reporting.

In general, CTCAE Guideline describes the Grades of AE severity from 1 to 5:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*

Grade 3: Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

***Instrumental Activities of Daily Living (ADL)** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

****Self-care Activities of Daily Living (ADL)** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: for Maculo-papular rash, only 3 CTC Grades exist:

Maculo-Papular Rash	
Definition: A disorder characterised by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.	
Grade 1	Macules/papules covering < 10% BSA with or without symptoms (eg, pruritus, burning, tightness)
Grade 2	Macules/papules covering 10 to 30% BSA, with or without symptoms (eg, pruritus, burning, tightness); limiting Instrumental Activities of Daily Living*; rash covering > 30% BSA with or without mild symptoms
Grade 3	Macules/papules covering > 30% BSA, with moderate or severe symptoms; limiting Self-care Activities of Daily Living **

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To assess the BSA affected by rash, please follow the algorithm described below:

Area	**Number of palms**	**Percent area**
Whole body	100	100%
Head and Neck	10	10%
Upper extremities	20	20%
Trunk	30	30%
Lower extremities	40	40%

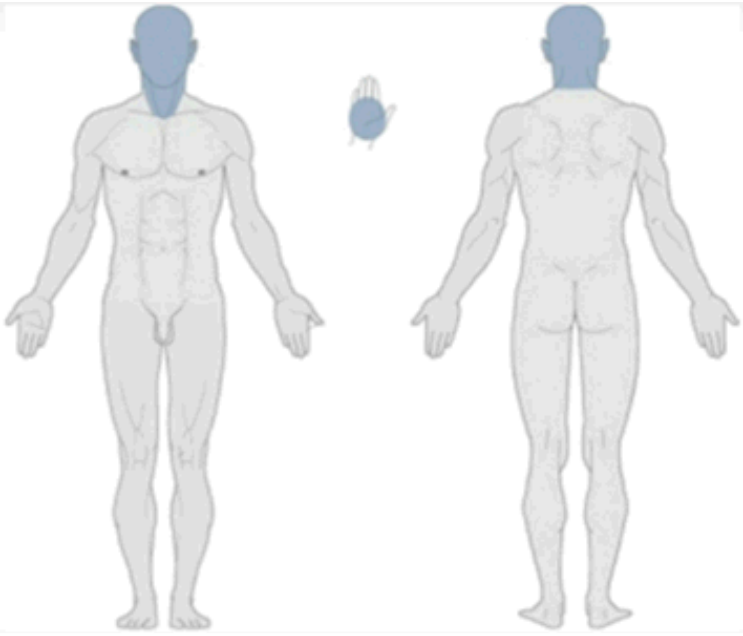
The participant's palm is defined as "1", representing 1% of total BSA.

Total BSA = 100% (100 palms).

The neck is included as part of the head

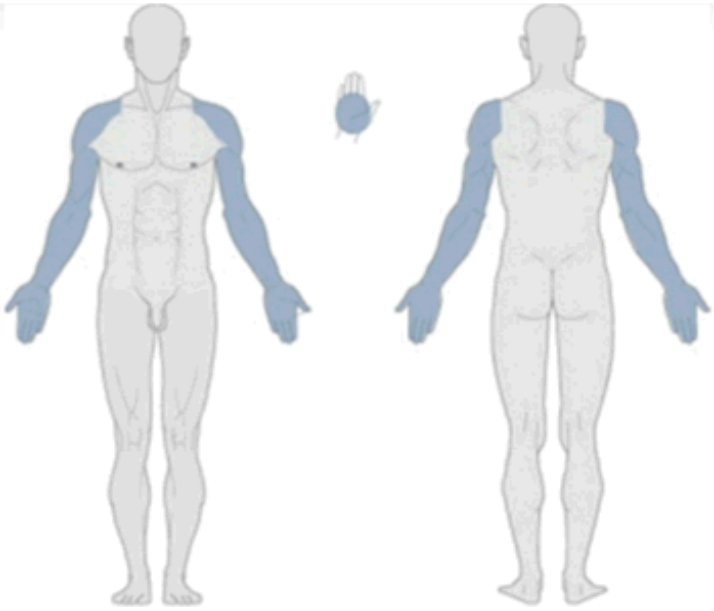
Head and Neck = 10% (10 palms)

Patient's palm = **1%**
Total BSA = **100%** (100 palms)



Upper extremities = 20% (20 palms)

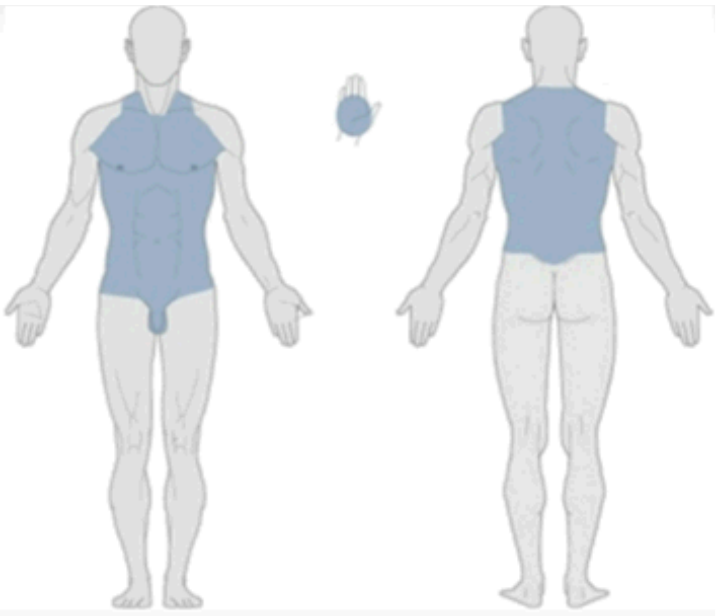
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



The axillae and genitals are included with the trunk

Trunk (axillae and groin) = 30% (30 palms)

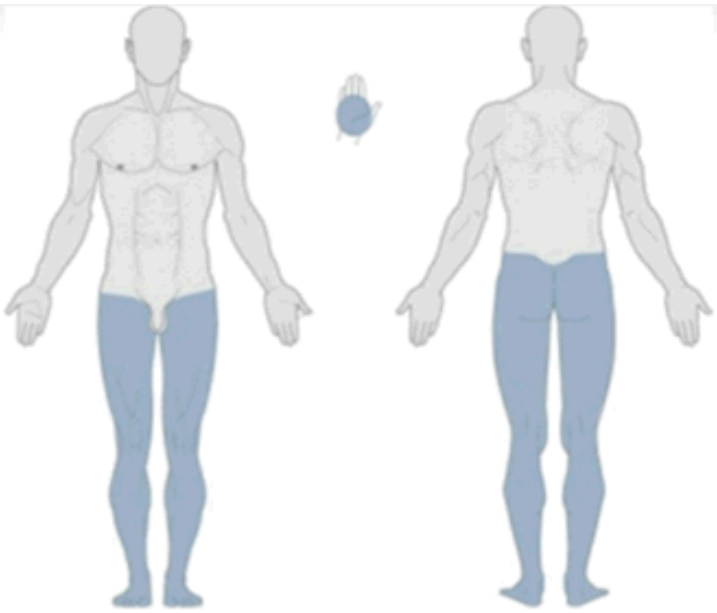
Patient's palm = **1%**
Total BSA = **100%** (100 palms)



The inguinal canal separates the trunk and legs anteriorly

Lower extremities (buttocks included) = **40%** (40 palms)

Patient's palm = **1%**
Total BSA = **100%** (100 palms)



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 during 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 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 Air Transport Association Guidance Document 62nd edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Air Transport 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 are 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.
- AstraZeneca 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:

- Non-leukocyte depleted whole blood transfusion within 120 days of optional genetic sample collection.

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 protocol.

Collection of Samples for Genetic Research

- One blood sample for DNA isolation will be obtained from the participants at Visit SV3 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 SV3, 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 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 subject 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 sample processing 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 or blood derivatives).
- 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 samples for analysis, facilitate correlation of genotypic, or multi-omics 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 genomics and multi-omics research component, are outlined in Appendix A.

Informed Consent

- The genomic and multi-omics component of this study are 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 PI(s) 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 participants, 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 potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law 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, potential Hy's Law 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 potential Hy's Law events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the IMP.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law 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 (AST) or Alanine Aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

For potential Hy's Law and Hy's Law 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 potential Hy's Law 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

Local Laboratories Being Used:

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets potential Hy's Law criteria (see Section E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

- Within 1 day of potential Hy's Law 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 protocol process for SAE reporting.
- For participants that met potential Hy's Law criteria prior to starting IMP, the investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition
- The Study Physician will contact the investigator, to provide guidance, discuss and agree an approach for the study participants' 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 laboratory kit should be used.
  - Complete the three 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 appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Physician will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. The AstraZeneca Global Study Physician 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 an 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 Hy's Law 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 the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol 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 Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol 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 Laboratory 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 & IgG anti-CMV IgM & IgG anti-HSV IgM & 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

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 CYP3A-Interacting Medication That Should be Avoided

Potent inhibitors and potent inducers of CYP3A4 should not be combined with mitiperstat (AZD4831) and should be stopped at least 14 days before the first dose of study intervention until 2 days after the last dose of study intervention.

The following are drugs known to be potent inhibitors and inducers of CYP3A4 (Table 8).

Table 8 is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4. For an updated list, please refer to the links below Table 8.

Appropriate medical judgment is required. The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Table 8 CYP3A-Interacting Medication That Should be Avoided

Medication	Recommendation	Rationale
Potent CYP3A4 inhibitors:		
Grapefruit juice	Should be avoided for 14 days prior to randomisation and for 2 days following discontinuation of mitiperstat (AZD4831)	Potent CYP3A inhibitors, which may increase mitiperstat (AZD4831) exposure
Macrolide antibiotics**:** clarithromycin, telithromycin, troleandomycin		
Azole antifungals: itraconazole, ketoconazole, voriconazole, posaconazole		
Antibiotics: chloramphenicol		
Nefazodone		
Potent CYP3A4 inducers:		
Carbamazepine	Should be avoided for 14 days prior to randomisation and for 2 days following discontinuation of mitiperstat (AZD4831)	Potent CYP3A inducers that can decrease mitiperstat (AZD4831) exposure
Fosphenytoin		
Rifapentine		
Phenytoin		
Primidone		
Rifampicin		
St. John’s wort		

Macrolide antibiotics can be used to treat pneumonia as soon as needed during study period, following temporary or permanent discontinuation of mitiperstat (AZD4831).
References:
FDA list of CYP3A inhibitors and inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
Flockhart Table: https://drug-interactions.medicine.iu.edu/MainTable.aspx
Metabolism & Transport Drug interaction database (DIDB) - Washington University: www.druginteractionsolutions.org

Appendix G EXACT Questionnaire

Table 1. Annotated EXACT® for Raw Score Assignment

The following annotates the raw item-level score values associated with each text response for the EXACT® items. Please take note of items with collapsed response scale scoring, highlighted in **bold.**

1. Did your chest feel congested today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
2. How often did you cough today?	0. Not at all
	1. Rarely
	2. Occasionally
	3. Frequently
	4. Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0. None at all
	1. A little
	1. Some
	2. A great deal
	3. A very great deal
	NOTE: Score "A little" and "Some" the same.
4. How difficult was it to bring up mucus (phlegm) today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Quite a bit
	4. Extremely
5. Did you have chest discomfort today?	0. Not at all
	1. Slight
	2. Moderate
	3. Severe
	4. Extreme
6. Did your chest feel tight today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely

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7. Were you breathless today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
8. Describe how breathless you were today:	0. Unaware of breathlessness
	1. Breathless during strenuous activity
	2. Breathless during light activity
	3. Breathless when washing or dressing
	3. Present when resting
	NOTE: Score "Breathless when washing or dressing" and "Present when resting" the same.
9. Were you short of breath today when performing your usual personal care activities like washing or dressing?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	4. Too breathless to do these
	NOTE: Score "Severely" and "Extremely" the same.
10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	3. Too breathless to do these
	NOTE: Score "Severely," "Extremely," and "Too breathless to do these" the same.
11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	3. Too breathless to do these
	NOTE: Score "Severely," "Extremely", and "Too breathless to do these" the same.

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12. Were you tired or weak today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
13. Last night, was your sleep disturbed?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	4. Extremely
14. How scared or worried were you about your lung problems today?	0. Not at all
	1. Slightly
	2. Moderately
	3. Severely
	3. Extremely
	NOTE: Score "Severely" and "Extremely" the same.

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Appendix H COPD Assessment Test (CAT)

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Appendix I Daily e-Diary

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Patient Reported Outcome Questionnaire was removed due to copyrights.

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Patient Reported Outcome Questionnaire was removed due to copyrights.

Appendix J 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 AstraZeneca.

J 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.

J 2 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 Standard Operating Procedures/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.

J 3 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.

J 4 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 K COVID-19 Specifics

K 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 the 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.

K 2 Risk Assessment for COVID-19 Pandemic

While there is a theoretical risk that treatment with an MPO inhibitor could impair host-defence mechanisms, an increased incidence of infection has not been seen in limited clinical data with mitiperstat (AZD4831). Therefore, the risk to participants exposed to SARS-CoV-2 or to those who suffer from COVID-19 is expected to be similar to the background population with the same comorbidities as those in the study. The risk of exposure to infected people cannot be completely excluded as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff and other participants of the clinical study).

AstraZeneca has no data on the co-administration of mitiperstat (AZD4831) and COVID-19 vaccines being approved. Potential mitiperstat (AZD4831) vaccine interactions affecting participant safety or IMP and vaccine efficacy are therefore unclear.

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

- Exclusion of participants with a significant COVID-19 illness within 6 months of enrolment defined as:

(a) A diagnosis of COVID-19 pneumonia based on radiological assessment.

(b) A diagnosis of COVID-19 with significant new findings from pulmonary imaging tests.

(c) A diagnosis of COVID-19 requiring hospitalisation and/or oxygen supplementation therapy.

- This study is going to start enrolling only when AstraZeneca deems 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 interventions 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 and on investigator's discretion.
  - Requesting all participants to be contacted by phone 1 day prior to every visit for assessing COVID-19 symptoms and signs and participants are asked not to attend the site in case of suspected reports (if appropriate, in accordance with local clinical guidelines). In addition, participants are asked for any contact with a person who has tested positive for SARS-CoV-2 (if appropriate, in accordance with local clinical guidelines). 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.
  - 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 AstraZeneca 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.

  - Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

- If site visits are not possible due to local restrictions, home nursing visits may be considered after discussion with and approval by AstraZeneca. Study intervention may be delivered direct to participant if appropriate and via AstraZeneca approved courier service.

K 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, according to local clinical guidelines prior to SV1 (screening), 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.

K 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.

K 5 References

Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 5 (10/02/2022).
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency, August 2021, Updated on January 27, 2021
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Appendix L Q-SAW Substudy

L 1 Substudy Synopsis

Background: A composite endpoint (COPDCompEx) for exacerbations is a novel endpoint that is being used as a surrogate efficacy endpoint for exacerbation risk reduction in randomised controlled trials. COPDCompEx captures AWEs, ie, clinically relevant deteriorations of PEF, reliever use or symptoms that fulfil specific criteria in terms of reaching thresholds or slopes. The Q-SAW substudy aims to provide a deeper understanding of day-to-day variations in symptoms and the impact of AWEs on the participant's life.

Objectives:

1 To evaluate the impact of an AWE on daily lives of patients with COPD

2 To identify and explain the AWE associated behaviours

Methods: A qualitative substudy will be conducted using a grounded theory approach (Strauss and Corbin 1994). Two semi-structured individual interviews will be conducted by video call or telephone call using open-ended questions, each of 30-minute duration. A topic list and interview guide with example questions will be used as a framework for the interviews (Appendix L 3).

Participant selection: Participants from selected sites in selected countries may be eligible for participation.

Participants who provided informed consent for this substudy may be invited for the initial interview after occurrence of an AWE. Study site personnel and interviewers will be instructed to avoid sharing information on the full study objectives and the procedure by which the participant will be selected for the interview in order not to influence the participant's recognition of having an AWE upon which any follow-up actions would be expected. Instead, participants will be informed that the aim of this substudy is to learn more about the impact of COPD on daily life. A second interview will be scheduled up to 6 weeks after the first interview when most participants are expected to have recovered from the AWE (Wageck et al 2019).

Selection of participants will continue until saturation in topics is achieved, which is expected to occur within a total of approximately 40 participants.

Methods of Analysis: Audio recordings of interviews will be transcribed and analysed with qualitative content analysis. Data will be coded and analysed by 2 researchers and consensus will be reached about potential discrepancies. Results will be systematically discussed with experts in the field. To achieve saturation in interview topics, data collection and coding will be done in an iterative manner. This allows for adaptation of the interview guide based on new

insights. The method of 'constant comparison' will be used for coding thereby expanding an initially defined coding tree (ie, according to the interview guide) with superordinate and subordinate themes.

L 2 Collection of Adverse Events During Participant Interviews

If a participant during the interview reports an AE, which occurred at any time, this will be recorded by the interviewer. For each AE the following variables will be collected:

- Participant details: Patient Ecode, Gender, Age.
- Treatment details: AstraZeneca product, Dose regimen, Date when treatment received.
- AE details: Description of AE (what experience), Date when the AE started and stopped, Whether the AE required any medical intervention (eg, hospitalization, medical treatment etc), Causality, Action taken with regard to medicinal product, Outcome.
- If follow-up is consented by the participant (Yes/No)
- Reporter information (name and contact information)
- Date/time of AE reporting
- Causality collection
- Causality assessment will be done by the participant. The interviewer will ask about causality during the interview ("Do you consider that there is a reasonable possibility that the event may have been caused by drug X?").

L 2.1 Reporting of Adverse Events During the Interviews

Participants will be encouraged to contact the clinical study team when AE or product complaints come up during the interview. The interviewer will ensure that all the necessary information is provided to the PI of the CRESCENDO study site. The PI will prompt GPRI if important or relevant information is missing. Follow-up is undertaken only if the participant has consented to be followed-up. If so, GPRI informs the PI of any follow-up information within the same timeframe as the original report.

In the event that GPRI and its Employees, during the course of performing the Services, become aware of an AE or other reportable safety information with or without an associated AE, (as defined by AstraZeneca's policies and the AE and other safety reporting training program) involving any AstraZeneca Group company product that is the subject of this Agreement, GPRI and its Employees are required to collect and submit within one business day from becoming aware, the appropriate information to AstraZeneca in accordance with AstraZeneca's policies, procedures, and any training provided by AstraZeneca. AstraZeneca is responsible for reporting AEs and other safety information to regulatory and government authorities.

L 3 Topics of Interview Guide

The interviews with participants will be centred around the following topics. Each interview will end with a reflection on discussed issues and potential omissions.

Topics First Interview
Current health status • Symptoms • Comorbidities • Management of COPD • Impact on daily task / responsibilities • Impact on relationships with family /friends
Perception of COPD symptoms and exacerbations • Variation in symptoms • Understanding the difference between typical and bad days in: – Mood – Daily activities and tasks – Duration relative to one another – Participant's perceived reasons
Reflection
Topics second interview
Current health status • Symptoms • Comorbidities • Management of COPD • Impact on daily task / responsibilities • Impact on relationships with family /friends
Health behaviour • Anticipation of exacerbations • Actions to control exacerbations
Barriers to reaching out

• Personal history with health care (in general) • Participant's opinion about health care
Reflection

L 4 References

Strauss and Corbin 1994
Strauss A and Corbin J. Grounded Theory Methodology: An Overview. in Handbook of Qualitative Research. 1994;273–285.

Wageck et al 2019
Wageck B, Cox NS, Holland AE. Recovery Following Acute Exacerbations of Chronic Obstructive Pulmonary Disease - A Review. COPD. 2019;16,93–103.

Appendix M SPFQ Substudy

M 1 Study Synopsis

This study will include an option for participants to complete a questionnaire, the SPFQ, which will give participants the opportunity to provide feedback on their clinical study experience. Participants will be asked to complete the questionnaire at the beginning, middle and end of the study in electronic format. Individual participant level responses will be anonymous to the investigator and site staff and so will not be reviewed by investigators. Coded responses will be used by the sponsor to understand participant experience on clinical studies and to identify where improvements can be made in the clinical study process. To do this, responses will be combined across studies and with data collected as part of the study, such as gender, ethnicity, and trial duration, to investigate correlations with the participant experience. Aggregated data may be shared, maintaining individuals' anonymity, with site staff so they can take steps to understand and improve the participant experience at their site. Data may also be compared with responses from other research partners/sponsors to better understand participant experience in clinical studies across the biopharmaceutical industry. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or adverse events and therefore would not be study data. Consequently, these data do not contribute to any endpoints on the study and will be analysed and reported separately from the clinical study data. The results of this participant experience analysis may be published or presented at scientific meetings, with the sponsor complying with the requirements for publication.

M 2 Study Participant Feedback Questionnaire

Patient Experience Initiative

Study Participant Feedback Questionnaire (SPFQ)

Version 1.0

Prepared by:

TransCelerate Patient Experience Initiative Team

This deliverable prepared by TransCelerate BioPharma can be adopted by member companies and others, but all adoption is purely voluntary and based solely on the particular company's unilateral decision. TransCelerate has provided this Study Participant Feedback Questionnaire ("SPFQ") and the corresponding User Guide (collectively the "Work Product") for informational purposes only. By using the Work Product, you manifest your assent to the terms of use set out in this paragraph. The Work Product are not tailored to any particular factual situation and are provided 'AS IS' WITHOUT WARRANTY OF ANY KIND, EITHER EXPRESSED OR IMPLIED, INCLUDING, BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF FITNESS FOR A PARTICULAR PURPOSE, NON-INFRINGEMENT, OR MERCHANTABILITY. TransCelerate and its members do not accept any responsibility for any loss of

any kind including loss of revenue, business, anticipated savings or profits, loss of goodwill or data, or for any indirect or consequential loss whatsoever to any person using the Work Product. Any party using the Work Product bears sole and complete responsibility for ensuring that the Work Product, whether modified or not, are suitable for the particular clinical trial, accurate, current, commercially reasonable under the circumstances, and comply with all applicable laws and regulations.

Section A: Your experience before you started the study <to be completed within 1 month of study enrollment>

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 5 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. I understand the treatment process in this trial (for example: when and how to take or use a treatment)	0	1	2	3	4
2. 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)					
3. 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)					
4. I felt comfortable that I could ask any questions before I joined the trial					

Section B: Your experience during the trial <to be completed during trial progress>

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 5 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1. 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
2. My trial visits have been well organized					
3. My trial visits are scheduled at a convenient time for me					
4. The staff treats me with respect					
5. I feel comfortable that I can ask questions during the trial					
6. I am satisfied with the answers I have received to my questions during the trial					
	No		Yes		
7. The time taken to collect data is acceptable to me (for example: in person visits, questionnaires, forms)					
8. The impact the trial has on my daily activities is acceptable (for example: household chores, work commitments, eating)					

Section C: Your experience at the end of the trial <to be completed at last trial visit>

Thank you for your participation. Your experiences in this trial are important to us and we would like to hear about them. Your answers will help us improve future trials. There are no right or wrong answers, and it will take approximately 5 minutes to complete. Your answers will be kept anonymous and will not impact your participation in this trial.

Please select **one** response for each item.	No		Yes		
1 . I was informed when I had completed the trial					
2 . 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
3 . 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
4 . 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
5 . Compared to when the trial started, the overall commitment required was similar to what I expected	0	1	2	3	4

Appendix N Patient Experience Interview Substudy

N 1 Synopsis

Background and Objectives: This substudy has two aims. First, to get more in-depth insight into the perceptions and experiences of participants on this study. This substudy complements the data of the quantitative SPFQ (Appendix M) and will be used to understand how participant experience can be improved in this study and in future studies. Secondly, it aims to gain further insight into the participant perceptions and experiences of the digital technology used in the study, including virtual spirometry.

Methods: Approximately 20 participants from selected sites will be invited to take part in a remote, semi-structured interview conducted over video call or telephone call. Overlap with Q-SAW substudy sites or participants will be avoided. The duration of the remote, semi-structured interview will be approximately 60 minutes. The timepoints of the interviews will be stratified over the study duration, starting after at least 2 study visits.

Methods of Analysis: The interviews will be recorded, transcribed, translated if applicable, and analysed with qualitative content analysis.

Please see Appendix L 2.1 for Adverse Event Reporting requirements for this substudy.

N 2 Interview Guide Themes

CRESCENDO-specific themes / topics	
Themes	**Example topics for each theme**
Spirometry / FEV1	• Usability/ease of use of virtual spirometry device • Experience connecting the device • The overall experience of virtual versus face-to-face spirometry • Acceptability of this data collection method • Acceptability of time taken to collect data
Digital patient solutions	• Unify usability/ease of use • Unify perceived value as a whole and perceived value of the specific features (e.g., notifications/reminders) • Attitude of using provisioned device versus using your own device • Acceptability of time taken to collect data • ePRO completion via smartphone (daily diary)
Visits	• Experience of preparing for and attending a o face-to-face visit o virtual visit • Perceived value of a o face-to-face visit o virtual visit • Attitudes and perceptions related to communication, comfort, trust
Non-financial impact	• Expected and actual time commitment • Impact on usual daily activities (eg work) • Impact on level of energy • Overall satisfaction
Motivation to participate	• What motivated the participant to enter the study? • What motivated the participant to continue with/complete the study?

General participant experiences themes / topics	
Themes	**Example topics for each theme**
Communication	• Experience with finding the study and getting the questions answered • Quality and clarity of communication from Sponsor and Site • Quality and sufficiency of the information provided to outline all the procedures and set the right expectations • Frequency of the communication • Acceptability of the channels used for communication • Ease of understanding the information provided, eg the ICF
Interactions with Staff	• Availability of staff • Perceived trust, respect, comfort with staff • Knowledgeability of staff
Study Site	• Location: ease of access, parking • Waiting room experience • Treatment area experience (e.g., comfort and privacy)
Financial impact	• Costs associated with participation in this study • Speed and sufficiency of the reimbursement of study-related expenses • Acceptability of the method of delivery of the reimbursement
Appreciation/Gratitude	• Did the participant receive any gratitude/appreciation? • (If yes) How was it? Did it make participants feel appreciated?
Experience joining the trial	
Previous trial experience vs Crescendo (If applicable)	How does this experience compare to the experience in other studies they may have participated in?

Open-ended questions about their experience	Anything else that they want to share related to their experience in this study (like/dislike/want to improve/remove)

Appendix O Protocol Version History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

CSP Version 4.0, 28 April 2023

This modification 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 and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

The primary rationale for the modifications in this CSP is to add the optional Q-SAW, SPFQ and patient experience interview substudies which affect only selected sites in selected countries where the substudies will be conducted. A substantial change was made to remove history of treatment with cardiotoxic medications from the list of exclusion criteria.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria.	Exclusion criterion 22 "History of treatment with cardiotoxic medications (eg, as part of cancer therapy) including thiazolidinediones such as rosiglitazone and pioglitazone" was removed and replaced with text: **This criterion has been removed.**	Previously included in error.

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Throughout.	Minor changes were made to formatting and wording throughout the document for example to fix errors and improve grammar and sentence/section structure without change of meaning.	To improve clarity and readability.
Throughout.	AZD4831 was changed to mitiperstat (AZD4831) throughout.	To align with other study regulatory documents.
Title page, Section 1.1 Synopsis.	The protocol title was changed: A Phase IIa Randomised, Double Blind, Placebo Controlled, Parallel Arm, Multi-Centre Study to Evaluate the Efficacy and Safety of **Mitiperstat (**AZD4831**)**, for 12-24 Weeks, in **Patients**	To include mitiperstat name and more accurately reflect the study objectives. The title change was considered to be a non-substantial change as it was not considered to have

Section Number and Name	Description of Change	Brief Rationale
	with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD).	a significant impact on the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints.	"Participants" was amended to "patients" as appropriate.	To clarify that the study participants included in this study are patients with moderate to severe COPD.
Section 1.1 Synopsis, Section 1.3 Schedule of Activities, Section 3 Objectives and Endpoints, Section 4.1.2 Q-SAW Substudy, Section 8.2.9 Q-SAW Substudy, Appendix L Q-SAW Substudy.	Details of the optional Q-SAW substudy were added throughout the protocol. New sections: Section 4.1.2, Section 8.2.9, and Appendix L were added.	To briefly outline the assessments and procedures for the optional Q-SAW substudy. The substudy affects only selected sites in selected countries where the substudy will be conducted. This is a non-interventional study and therefore considered to be a non-substantial change.
Section 1.1 Synopsis, Section 1.3 Schedule of Activities, Section 3 Objectives and Endpoints, Section 4.1.3 SPFQ Substudy, Section 8.2.10 SPFQ, Appendix M SPFQ Substudy.	Details of the optional Study Participant Feedback Questionnaire (SPFQ) were added throughout the protocol. New sections: Section 4.1.3, Section 8.2.10, and Appendix M were added.	To briefly outline assessment and procedures for the optional SPFQ substudy. The substudy affects only selected sites in selected countries where the substudy will be conducted. This is a non-interventional study and therefore considered to be a non-substantial change.
Section 1.1 Synopsis, Section 1.3 Schedule of Activities, Section 3 Objectives and Endpoints, Section 4.1.4 Patient Experience Interview Substudy, Section 8.2.11 Patient Experience Interview Substudy, Appendix N Patient Experience Interview Substudy.	Details of the optional patient experience interview substudy were added throughout the protocol. New sections: Section 4.1.4, Section 8.2.11, and Appendix N were added.	To briefly outline the assessments and procedures for the optional patient experience interview substudy. The substudy affects only selected sites in selected countries where the substudy will be conducted. This is a non-interventional study and therefore considered to be a non-substantial change.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints.	Alteration to primary objective: "To evaluate the effect of AZD4831 as compared to placebo on the time to first COPDCompEx event **in participants with moderate to severe COPD**."	To be consistent with the style of the other objectives.

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints.	For secondary objective: To assess the effect of AZD4831 compared with placebo on post-BD FEV1 in participants with moderate to severe COPD, the estimand text was amended: "~~Strategy for intercurrent events~~ **Primary estimand**: **while on treatment**. **Supportive estimand:** treatment policy." For secondary objective: To assess the effect of AZD4831 compared with placebo on respiratory symptoms in participants with moderate to severe COPD, the estimand text was amended: "Strategy for intercurrent events: **while on** treatment ~~policy~~." For the secondary objective: To assess the effect of AZD4831 compared with placebo on disease impact in participants with moderate to severe COPD, the estimand text was amended: "Strategy for intercurrent events: **while on** treatment ~~policy~~."	To clarify the wording of the estimands for the secondary objectives.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, Section 8.2.1 COPDCompEx and Section 8.2.2.1 Assessment of COPD Exacerbation.	**"An episode of pneumonia"** added to list as an exacerbation.	To align with the revised COPDCompEx Business Rules (dated 13 April 2023), where an episode of pneumonia is now included as an exacerbation, not a dropout due to efficacy.
Section 1.1 Synopsis, Section 4.1 Overall Design.	Text amended "It will be performed in approximately 100~~-101~~ sites..."	Wording change to show a more approximate number. This is not a change to study design.
Section 1.1 Synopsis, Section 1.2 Schema, Section 4.1 Overall Design, Section 4.2 Scientific Rationale for Study Design, Section 7.1.4 Participant Discontinuation at Study End, Section 9.4.2.1 Primary Endpoint.	Text relating to the end of study in Sections 1.1, 1.2, 4.1, and 7.1.4 was changed: ~~Once the last participant has completed 12 weeks of treatment, the study can stop. At this point, all participants still receiving treatment should attend Study Visit SV7 as soon as possible, continuing treatment until they do. They should then attend SV8 14 ± 3 days later. These SV7 visits can be planned in anticipation of the last participant completing 12 weeks of treatment, but must not be performed~~	To clarify the study discontinuation process.

Section Number and Name	Description of Change	Brief Rationale
	~~before that date. The last participant can combine SV5 and SV7 in one visit, then attend SV8 14 ± 3 days later.~~ **Enrolment will be stopped after at least 113 first COPDCompEx events have occurred. At this point, all participants enrolled in the study that have not yet completed SV5 should continue in the study to complete 12 weeks of treatment. For these participants SV5 and SV7 should be combined into one visit. Participants who have already completed 12 weeks of treatment when study enrolment is stopped should attend SV7 as soon as possible, continuing treatment until they do. All participants should attend SV8 14 ± 3 days after SV7.** Minor changes were made to the text in Sections 4.2 and 9.4.2.1 to reflect this change.	
Section 1.3 Schedule of Activities.	Visit timepoint SV7 changed to SV7/EDV and associated footnote added for explanation.	To clarify that this timepoint could be SV7 or EDV. No change to the study procedure.
Section 1.3 Schedule of Activities, Section 8.2.7 Computed Tomography Scan.	Details for high resolution CT scan amended: The high resolution CT ~~can~~ **could** be performed ~~within ± 2 weeks of SV3~~ **as soon as main eligibility criteria are confirmed at SV1 which include blood test result, up to randomisation. The local CT scan report must be obtained before randomisation.** These details were also added to Section 8.2.7.	To clarify the timing of the study procedure.
Section 1.3 Schedule of Activities.	The R denoting the timepoint at which the device for e-Diary should be returned was moved from SV8 to SV7. A footnote was added to explain that the morning and evening diaries that include cough VAS and BCSS start the day after SV2. Notes were added to explain that e-Diary and PEF, Cough VAS assessment and BCSS (daily) will be recorded up until the day of SV7 or EDV.	To clarify the timing of the study procedures.
Section 5.2 Exclusion criteria.	Exclusion criteria 3(e) amended: Systemic hypertension, except if well controlled ~~using 2 or fewer medications and stable for~~	To clarify the details of the exclusion criteria related to systemic hypertension.

Section Number and Name	Description of Change	Brief Rationale
	~~at least 6 months~~ **and stable for at least 3 months in the opinion of the investigator**.	
Section 5.2 Exclusion criteria.	Exclusion criteria 9 amended: Any history of lung volume reduction surgery**, including endoscopic lung volume reduction procedure with endobronchial valves**.	To clarify lung volume reduction procedure that would exclude participant from the study.
Section 6.1 Study Intervention(s) Administered.	Dose formulation for AZD4831 and placebo changed from tablet to film-coated tablet.	For accuracy and consistency with other study documentation.
Section 7.2 Participant Discontinuation/Withdrawal from the Study, B 5 Guide to Skin Reaction Assessment.	The wording "early treatment discontinuation visit" was changed to "early discontinuation visit."	For document consistency. There is no change to the meaning.
Section 8.2.7 Computed Tomography Scan.	The Computed Tomography Scan section was moved from Section 8.3.5 to Section 8.2.7. As a result, Section 8.2.7 Cough Substudy and Section 8.2.7.1 VitaloJAK® Cough Monitor Device were moved to Section 8.2.8 and Section Section 8.2.8.1 respectively. Section 8.3.6 SARS-CoV-2 Screening was moved to Section 8.3.5.	The assessment is considered to relate to efficacy rather than safety.
Section 8.2.7 Computed Tomography Scan.	Addition of text: **The CT scan will be performed to characterise and assess the severity of COPD at baseline by, among other approaches, evaluation of the distribution of emphysema and visualisation of small airways disease, mucous plugging and/or bronchiectasis. It is anticipated that a more detailed analysis of responders to treatment will be done on the basis of pre-existing emphysema severity and the presence of mucous plugging in particular. This may guide the inclusion of patients in the subsequent development program and will also be used to explore the association with the other biomarkers of disease progression from both blood and sputum biomarker sampling.**	To justify the CT scan assessment.
Section 8.8.1 Mandatory Biomarker Sample Collection.	Footnote added to note that each of the applicable blood sample assessments "Will	To specify and clarify the biomarker samples and assessments and to clarify that

Section Number and Name	Description of Change	Brief Rationale
	not be delivered prior to database lock and will not be part of the CSR." Specification that sputum samples will be collected to assess "MPO concentration and activity" and "other" markers of inflammation and neutrophil activation.	some sample assessments will not be included in the CSR.
Section 9.3 Populations for Analysis.	The description of the cough subset population for analysis was amended "Will include the subset of ~~PP set~~ **FAS** who consented to the cough substudy." A new analysis set "Randomised Set" was added to the populations for analysis table with the description "Will include all participants who have been randomised."	To outline the populations for analysis.
Section 9.4.3 Safety.	Treatment emergent heading and text removed from safety statistical analysis section. ~~The definition for treatment emergent events will be provided in the SAP.~~	This was included in the previous version in error. This is not detailed in the SAP.
Section 9.4.3 Safety.	Text in laboratory parameters statistical safety section amended: "A frequency table presents **the** number of participants reporting at least one **abnormality** ~~treatment emergent change~~ in selected laboratory parameters."	To correct inaccuracies in the statistical analysis procedures.

Bold signifies added text, strike through signifies deleted text.

CSP Version 3.0, 13 January 2023

This modification 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 and in the EU Clinical Trial Regulation Article 2, 2 (13).

Overall Rationale for the Modification:

The primary rationale for the modifications in this CSP is to add clarity and detail to the study procedures and avoid ambiguity. Changes were also made in response to the requirements of various health authorities. A substantial change was made to adapt to changes in SARS-CoV-2 screening requirements.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criteria 1 removed and replaced with text: "**This criterion has been removed."** ~~Participants with a positive diagnostic lateral flow test for SARS-CoV-2 at SV1 or SV3. Participants will be eligible for rescreening ≥ 2 weeks after a positive SARS-CoV-2 lateral flow test once COVID-19 symptoms have resolved, at the investigator's discretion (see Section 5.4).~~"	To confirm the change in requirement for SARS-CoV-2 screening during the study. Positive SARS-CoV-2 test at SV1 and SV3 is no longer an exclusion criterion. This is to be in line with local requirements in most countries in which SARS-CoV-2 screening is no longer mandatory.

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
Throughout	CSP template updates were amended throughout except for Objectives and Endpoints (Synopsis and Section 3). Amendments included changing wording of "Sponsor" to "AstraZeneca" and "patient" or "subject" to "participant". Sections were added, removed, or amended in accordance with template updates. New section headings in this version compared with the previous CSP version include: 5.5 Criteria for Temporarily Delaying Enrolment, Randomisation, or Administration of Study Intervention 6.1.1 Medical Devices Including Combination Products with a Device Constituent 6.3 Assignment to Study Intervention 6.4 Blinding 6.8 Treatment of Overdose 8.1 Administrative and General/Baseline Procedures 8.2.2.3 Duration of AECOPD 8.3.6 SARS-CoV-2 Screening 8.4.12 Reporting of Overdose 8.10 Study Participant Feedback Questionnaire	The CSP was updated in line with the latest AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0.

Section Number and Name	Description of Change	Brief Rationale
	In addition, several section numbers have changed, particularly from Section 6 onwards.	
Throughout	Minor changes were made to formatting and wording throughout the document for example to fix errors and to improve grammar and sentence/section structure without change of meaning.	To improve clarity and readability.
Title page	"Short Title" changed to "**Brief Title**" and changed from "12 to 24 weeks of AZD4831versus placebo for treatment of moderate to severe chronic obstructive pulmonary disease" to **"An Efficacy and Safety Study of AZD4831 (MPO Inhibitor) vs Placebo in the Treatment of Moderate to Severe COPD"**	To align with the brief title used on ClinicalTrials.gov, which is also in accordance with AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0.
1.3 Schedule of Activities, 5.4 Screen Failures	Since exclusion criteria 1 has been removed, SARS-CoV-2 test (at SV1 and SV3) removed from SoA. Text removed from Section 5.4 as Screen Failures as no longer relevant: "~~A positive SARS-CoV-2 lateral flow test. Participants will be eligible for rescreening ≥ 2 weeks after a positive SARS-CoV-2 lateral flow test once COVID-19 symptoms have resolved, at the investigator's discretion.~~"	To confirm and clarify the change in requirement for SARS-CoV-2 screening during the study. Positive SARS-CoV-2 test at SV1 and SV3 is no longer an exclusion criterion. This is to be in line with local requirement in most countries in which SARS-CoV-2 screening is no longer mandatory.
1.1 Synopsis, 3 Objectives and Endpoints	Secondary objective for cough substudy: "To assess the effects of AZD4831 compared to placebo on change in cough frequency measured over a 24-hour period between **start of treatment** and Week 12" corrected to exploratory objective. Due to template update, only primary and secondary objectives and endpoints are included in synopsis; therefore, removed from synopsis. The wording of "baseline" changed to "**start of treatment**".	Correction of endpoint of the cough substudy from secondary to exploratory, as the substudy is an exploratory study and hence the endpoints would not be considered secondary. This does not impact the scientific value of the main study or the substudy. Start of treatment is used in place of baseline to clarify the time of study measure.
1.1 Synopsis, 3 Objectives and Endpoints	Text moved from table to footnotes: "**Intercurrent events are events occurring after treatment initiation (eg,**	Clarification of intercurrent events in the study.

Section Number and Name	Description of Change	Brief Rationale
	discontinuation of treatment, switching treatment, terminal events such as death) that affect either the measurement or interpretation of the summary measure (eg, hazard ratio) associated with the clinical question of interest. Addition of text: "**This study contains 2 intercurrent events:** **1) Treatment discontinuation (with the following reasons: SAE, death not due to exacerbation, COVID-19, pneumonia, other).** **2) Prohibited medication.**"	
1.1 Synopsis, 4.1 Overall Design	Update to the approximate number of study sites (from 143 to 101) and countries (from 12 to 14). Text amended in Section 4.1: "This is a Phase IIa, randomised, placebo-controlled, double-blind, parallel-arm, event-driven study with an up to 24-week treatment time**. It will be performed in approximately 101 sites across approximately 14 countries. It is** designed…"	Update to study logistics. This does not impact number of participants and does not have a significant impact on safety or scientific value of the study.
1.1 Synopsis, 1.3 Schedule of Activities, 2.3.2 Benefit Assessment, 3 Objectives and Endpoints, 8.2.4 Participant-Reported Outcomes, 8.2.6 E-Diary, Appendix G EXACT Questionnaire	Patient reported outcome questionnaire changed from E-RS:COPD to EXACT throughout and copy of EXACT added in Appendix G.	Due to requirement to use the full 14-question EXACT Scale by the license holder. ERS:COPD is similar to EXACT, therefore this change would not affect the safety and scientific value of the study.
1.1 Synopsis, 9.5 Interim Analysis, 9.6 Data Review Committee Appendix A5 Committees Structure	Updates to clarify that the URC will be responsible for conducting the administrative IA and the DRC will be responsible for safety monitoring.	To simplify/clarify the roles of the URC/DRC.
1.1 Synopsis, 4.1 Overall Design	Change of wording related to SV6 (virtual visit) from "will be performed at the participant's home" to "will be performed **away from the study site.**"	Clarification of acceptable locations for study virtual visit.
1.2 Schema, 1.3 Schedule of Activities	Change to the wording for SV1 and SV2. SV1 wording amended from "Day -28 to -1" to "**Day -28 to -14**." SV2 wording amended from "Day -14 (-2)" to "**Day -16 to -14.**"	To clarify the study visit window wording and ensure compliance according to inclusion criterion 7 (SV2 must be completed 14 days preceding SV3 to ensure

Section Number and Name	Description of Change	Brief Rationale
		eDiary/PEF compliance according to inclusion criterion 7, therefore SV1 required to be completed by Day -14).
1.3 Schedule of Activities, 4.1 Overall Design	Footnote (a) added for SV6 (virtual visit) in SoA: "**For virtual visit of SV6, this will be conducted over telemedicine video conferencing facility based on technology provided by Zoom Inc (San Jose, California, USA), through the UNIFY platform, using a provisioned handheld device.**" Text added to overall design: "**This will be conducted over the same telemedicine video conferencing facility that is being used for the virtual spirometry during other visits in the study and is based on technology provided by Zoom Inc (San Jose, California, USA), through the UNIFY platform, using a provisioned handheld device.**"	Detail to clarify how the SV6 virtual visit will be performed.
1.1 Synopsis, 4.1 Overall Design	Text amended: "MPO level and activity in sputum at Week 12 compared to ~~Week 1~~ **baseline**, and symptom scores."	Clarification of secondary efficacy assessment timepoint (not a change of timepoint).
1.3 Schedule of Activities	Clinical spirometry (post-BD) site measurement added at SV4.	To align with other site visits.
1.3 Schedule of Activities	Text added to notes for clinical spirometry (post-BD) procedure: "**Screening spirometry at SV1 will be conducted using the spirometry equipment supplied to clinic.** **In the event that an adequate quality, maximal effort spirometry effort cannot be obtained at the first attempt during a study visit, a further reattempt is allowed (see Section 8.2.3)**."	To clarify the clinical spirometry (post-BD) procedure and to determine the criteria for when reattempt is permitted at SV1.
1.3 Schedule of Activities, 5.1 Inclusion Criteria, 8.2.6 E-Diary	Text added to e-Diary and PEF procedure notes (Schedule of Activities), inclusion criterion 7 and e-Diary section to define compliance and to detail the steps to take should adherence drop below 80% to 85%.	To clarify the compliance procedures in the study.
1.3 Schedule of Activities, 8.6.1 Collection of Samples for Pharmacodynamics	Added text to both sections related to blood sample for target engagement assay: "**In a subsample of approximately 60 participants in selected countries**."	To clarify that systemic target engagement assay is not required for all participants.

Section Number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Text: "**EDV only**" added for PK blood sampling for AZD4831 procedure at SV7.	To clarify timing of PK blood sampling for AZD4831 at early discontinuation visit.
2.3.1 Risk Assessment, 2.3.3 Overall Benefit/Risk Conclusion, 3 Objectives and Endpoints, 7.1.2 Temporary Discontinuation, 7.1.3 Restarting After Temporary Discontinuation, 8.4 Events, AEs, SAEs, and Other Safety Reporting, 8.4.9 Adverse Events of Special Interest	Text amended to "**serious** infection" where appropriate.	To clarify serious infection rather than any infection.
3 Objectives and Endpoints	Text added: "MPO- and neutrophil- related circulating **and nasal mucosal lining fluid** biomarkers."	To clarify that nasal lining fluid biomarkers will be one of the exploratory endpoints as the samples will be collected from the participants as per SoA.
3 Objectives and Endpoints	Exploratory spirometry objective and endpoints added to Table 3: Objective: To assess the effects of AZD4831 as compared to placebo on spirometry endpoints measured face-to-face and virtually in participants with moderate to severe COPD endpoints: spirometry endpoints, including but not limited to, FEV1, forced vital capacity, forced expiratory flow 25% to 75%, inspiratory capacity, and reproducibility	These spirometry endpoints are being collected in the previous version of protocol. The objectives and endpoints were added to clarify the intention to analyse these data, in an exploratory manner. This does not have a significant impact on safety and scientific value of the study.
3 Objectives and Endpoints	Exploratory objective and endpoints added to measure effect of sputum MPO concentration: **Objective: To assess the effect of sputum MPO concentration at baseline on primary and secondary endpoints in participants with moderate to severe COPD.** **Endpoints:** **Time to first COPD CompEx event in participants with low MPO concentration at baseline compared to high MPO concentration at baseline.**	To clarify intended exploratory analysis for sputum MPO concentration. This does not have a significant impact on safety and scientific value of the study.

Section Number and Name	Description of Change	Brief Rationale
	Change from baseline post-BD FEV1 in participants with low MPO concentration at baseline compared to high MPO concentration at baseline.	
5.1 Inclusion Criteria	Added text to inclusion criterion 5: "Participants who have a documented stable regimen of triple therapy or dual therapy for ≥ 3 months prior to enrolment **(change of inhaler device or change of medication in the same drug class is allowed).**"	To clarify the details of the inclusion criterion related to therapy.
5.1 Inclusion Criteria, 8.4.10.2 Paternal Exposure	Contraceptive period for males updated from 90 to 105 days and text amended for inclusion criterion 10a: "Male patients must be surgically sterile **(eg, vasectomy with confirmed azoospermia)**…"	To ensure the global protocol is suitable for all country-specific requirements and to clarify specific detail.
5.1 Inclusion Criteria	Inclusion criterion 10a amended: "For a non-pregnant woman of childbearing potential partner, contraception recommendations should also be considered. Acceptable methods of contraception ~~include~~ **are** birth control pills, injections, implants, or patches, intrauterine devices, and tubal ligation/occlusion. A barrier method is not necessary if the female partner is sterilised. **All other contraceptive methods are considered unacceptable.**"	To clarify specific details of inclusion criterion 10a as per request from Spanish Health Authority to ensure the global protocol is suitable for all country-specific requirements.
5.2 Exclusion Criteria	Exclusion criterion 3 updated to "SV1 [screening] ~~and~~ **through to** SV3 [pre-dose]"	To clarify that SV2 is also included since it is part of the screening period.
5.2 Exclusion Criteria	Exclusion criterion 4c wording amended: "A diagnosis of asthma made when the participant was aged ≥ 40 years, confirmed by the investigator to be a misdiagnosis **on the basis of objective testing** ~~after discussion with and agreement of the AstraZeneca Study Physician~~." Exclusion criterion 23 wording amended: "Major surgery within 8 weeks prior to screening or planned inpatient surgery or hospitalisation during the study period. ~~Elective hospitalisations that cannot be delayed until after the end of the study need to be discussed with the sponsor's medical monitor~~."	Exclusion criteria 4c and 23 were updated to remove the need for Sponsor involvement in eligibility determination, as per Good Clinical Practice ICH E6(R2), Section 4.3.1, as per request from the UK Health Authority.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Exclusion criterion 7 wording updated to add that any of the criteria listed would lead to exclusion from the study, including previous hepatic imaging or pathological sampling.	To clarify exclusion criterion 7 and to ensure further guidance is given to the investigator, as per request from German Health Authority.
5.2 Exclusion Criteria	Exclusion criterion 7(g) updated to "Chest CT scan findings requiring further investigation ~~other than surveillance CT scan(s)~~ **or repeat CT surveillance scan before SV8**."	For consistency with Section 8.3.5 Computed Tomography Scan.
5.2 Exclusion Criteria	Exclusion criterion 21 wording amended: "Participants currently receiving background therapy for COPD that is not approved by regulatory authorities in the country of study (with the exception of nicotine vaping products, long-term azithromycin, erythromycin **and/or** ICS ~~monotherapy~~ **standalone inhaler [as part of triple or dual therapy]** of at least 3 months' duration)**.**"	To clarify acceptable ICS therapy.
5.2 Exclusion Criteria	Exclusion criterion 21 wording amended: "Treatment with broad spectrum antibiotic (excluding long-term azithromycin or erythromycin **as mentioned in exclusion criterion 21**) within 4 weeks prior to randomisation (Day 1)."	To clarify exceptions to the excluded antibiotic treatment.
5.2 Exclusion Criteria, 6.9 Prior and Concomitant Therapy	Exclusion criterion 28(e) wording amended: "Live, attenuated, or mRNA vaccines within 2 weeks **prior to** ~~of~~ SV1 **only**." Addition of text relating to vaccines in section 6.9: "Live, attenuated, or mRNA vaccines **if within 2 weeks prior to SV1 only**."	To clarify that live, attenuated or mRNA vaccines are not permitted only within the 2-week period prior to SV1.
5.2 Exclusion Criteria, 6.9 Prior and Concomitant Therapy	Addition of carbimazole and methimazole to prohibited medications listed in exclusion criterion 28(e) and Section 6.9.	To clarify further drugs (for hyperthyroidism) which are prohibited from the study.
5.3.1 Meals and Dietary Restrictions	St John's wort added to list of restrictions.	To clarify that participants should not consume St John's wort during study.
6.1.1 Medical Devices Including Combination Products with a Device Constituent, Appendix B 5,	Inclusion of text defining the use of ZEPHYRx and/or Medidata as appropriate.	To clarify the applications used.

Section Number and Name	Description of Change	Brief Rationale
Guide to Skin Reaction Assessment		
6.1.1 Medical Devices Including Combination Products with a Device Constituent	Addition of the type of spirometer: MIR Spirobank II Smart for SV1 screening only. Addition of text "**(available in each study region)**" for medical devices: MIR Spirobank Smart spirometer, MIR Spirobank II Smart spirometer and VitaloJAK® cough monitor.	To specify the medical devices used in the study and their availability.
6.3 Assignment to Study Intervention	Text amended: Before the study is initiated, ~~the telephone number and call in directions for the IRT and/or~~ the log in information and directions for the IRT/RTSM will be provided to each site.	Telephone number and call in details removed as not relevant.
6.4 Blinding	Creation of new section 6.4, 'Blinding' and text added: "**The study will be blinded to both participants and investigators/site staff as well as to AstraZeneca staff. With the formation of the URC and DRC (see Appendix A 5) the study will become unblinded to the AstraZeneca staff assigned to these committees (including those with clinical, medical, statistical, and programming expertise) who will form a firewalled URC for administrative purposes and will all be independent from the study team (see Appendix A 5). The URC will be responsible for conducting the administrative IA whereas the DRC will be responsible for safety monitoring.**"	In accordance with AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0 and to simplify/clarify the roles of the URC/DRC.
6.8 Treatment of Overdose	Text added to new section including: "**Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted.**"	In accordance with AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0 and to clarify the study procedure.
7.1.2 Temporary Discontinuation	Text added: "**The treatment period will not be extended to compensate for the temporary discontinuation.**"	To clarify the study procedure.
7.1.2 Temporary Discontinuation	New text added: "**In case of 'unconfirmed pneumonia', if the participant is not hospitalised and/or does not have a chest**	To clarify the study procedure.

Section Number and Name	Description of Change	Brief Rationale
	x-ray confirming diagnosis of pneumonia, this should generally be considered an infective exacerbation of COPD rather than pneumonia. In this scenario, study intervention can continue. If the investigator still considers this to be pneumonia, then discussion with the AstraZeneca medical monitor would be needed regarding continuation/discontinuation of study intervention. **In case of serious infection, the study intervention should be immediately discontinued on a temporary basis, unless any permanent discontinuation criteria are met (Section 7.1). After discontinuation of study intervention, any appropriate treatment is allowed if conditions presented in Section 6.9 are met.** **Study intervention does not need to be stopped for antibiotic treatment of non-serious infection."**	
7.2 Participant Discontinuation/Withdrawal from the Study	Text added to discontinuation section: "**At the time of discontinuation from the study, if possible, SV7, as an early treatment discontinuation visit, should be conducted, as shown in the SoA (Table 1). See the SoA 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.**	To clarify the study procedure and to be consistent with paragraph below regarding participant withdrawal.
8.2.1 COPDCompEx	The COPDCompEx definition was updated to include corticosteroid injection.	To clarify that corticosteroid injection is defined as a COPDCompEx event.
8.2.2.3 Duration of AECOPD	Section added to this version of the protocol in line with template.	In accordance with AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0 and to

Section Number and Name	Description of Change	Brief Rationale
		define the start and stop dates of AECOPD.
8.2.3 Spirometry and Peak Expiratory Flow Measurement	Amendment of text: "Where sites do not have access to such device, **they will be provided with an MIR Spirobank II Smart and android tablet with ZEPHYRx KIOSK mode application. This device and application shall only be used for screening spirometry performed at SV1**~~, an appropriate spirometer will be provided~~."	To clarify the study procedure and devices.
8.2.3 Spirometry and Peak Expiratory Flow Measurement	Text added: "**In the event that an adequate quality, maximal effort spirometry effort cannot be obtained at the first attempt during a study visit, a further reattempt is allowed. The participant should be rested for a period of time deemed appropriate by the investigator and have recovered sufficiently for the procedure to be completed safely. This will not be considered rescreening if undertaken on the same day as the first attempt.**"	To clarify that reattempt of spirometry assessment at screening visit is permitted for borderline results.
8.2.3 Spirometry and Peak Expiratory Flow Measurement	Change of wording related to SV3, SV4, SV5 and SV7 to make it clearer where and when virtual and face-to-face spirometry assessments will be performed.	To clarify acceptable locations for study virtual spirometry assessments and to clarify the study procedure for face-to-face and virtual spirometry assessments.
8.2.7.1 VitaloJAK® Cough Monitor Device	Text added "**The participants will be asked to return the device to site after completion of recording as soon as feasible. At some sites, the participants will also have the option of having the device collected, eg, by courier.**"	To clarify study procedures.
8.3.2 Vital Signs	Removed the text stating the orthostatic BP measured at SV3 will be reviewed by the unblinded DRC.	Included in error in previous version.
8.3.4 Clinical Safety Laboratory Tests	"**Thyroid stimulating hormone (TSH)**" added to Table 6 under "Thyroid Tests" heading.	Missing from previous protocol version in error.
8.3.5 Computed Tomography Scan	Text amended: "All new CT scans should be performed post-BD~~, ie, within 60 minutes of using up to 4 inhalations of albuterol or salbutamol~~ **which includes the**	To clarify the procedure for CT scans and for consistency with Section 8.2.3 Spirometry and Peak Flow Measurement.

Section Number and Name	Description of Change	Brief Rationale
	participant's regular triple or dual (ICS + LABA or LAMA + LABA) therapy. When these are undertaken at the same visit as spirometry ~~and small airway measurements~~, **the** CT should be performed after these assessments.~~, so as not to confound the BD withhold periods. If BD is performed as part of the spirometry assessments, this should be repeated if the BD occurred in excess of 60 minutes prior to the CT scan.~~"	
8.3.5 Computed Tomography Scan	Addition of "**/or**" to text: "The participant has not had an inspiratory and/**or** expiratory chest CT scan within 6 months of informed consent"	To add clarification.
8.3.6 SARS-CoV-2 Screening	New section with text: "**A SARS-CoV-2 (COVID-19) screening test can be performed at the time of study visits if required by local clinical guidelines for the safety of site staff and other site attendees but otherwise is not mandated in the study.**"	Following removal of SARS-CoV-2 screening test Exclusion Criteria 1, this is added to accommodate those countries which still need the test as per local clinical guidelines.
8.4 AEs, SAEs, and Other Safety	Addition of AE variable for maximum CTCAE grade for non-maculopapular rash (in addition to maculopapular rash) and clarification of wording that CTCAE Grades for maculopapular and non-maculopapular rash will be captured.	To align with the eCRF and clarify that CTCAE Grade will be collected for maculopapular and non-maculopapular rashes.
8.4.9 Adverse Events of Special Interest	Text amended: "It is suggested to start ~~the~~ treatment ~~with~~ **for maculopapular rash, per local standard treatment guidelines (which may include, but not be limited to,** a topical steroid and/or oral antihistamine**)**" Addition of text: … should be uploaded to the **Medidata** imaging portal… "	To clarify the study procedure and application used.
8.4.10.2 Paternal Exposure	Text added: "**In case of pregnancy in the partner of a male participant, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to**	To clarify the study procedure.

Section Number and Name	Description of Change	Brief Rationale
	be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should, if possible, be obtained and documented."	
8.4.13 Medical Device Deficiencies	Text amended from "In this study any deficiency observed with a third-party medical device will be collected and reported to the manufacturer." to "**In this study any deficiency observed with a third-party medical device will be reported directly to the third-party manufacturer by the study site staff according to the contact details in the device Instructions For Use**"	To clarify the procedure in the event of a deficiency with a third-party medical device.
8.5 Pharmacokinetics	Removal of US and UK wording related to 20% of patients to have additional post-dose PK samples.	To clarify this may not be limited to patients in the US and UK.
8.8.1 Mandatory Biomarker Sample Collection	Sputum colour removed.	Not required as part of sputum sample assessment.
8.8.2 Mandatory Genetic Analysis Sample Collection	Text amended: "Genotyping will ~~include, but will not~~ be limited to an assessment of the HLA genes. ~~The genetic research may involve the genotyping of selected genes or the analysis of the whole genome sequence.~~ The sample will only be used for these purposes as outlined."	To clarify the study procedure.
Appendix A 1 Regulatory and Ethical Considerations	Addition of section "Regulatory Reporting Requirements for Serious Breaches" in line with template.	In accordance with AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0.
Appendix A 7 Data Quality Assurance	Storage of records and documents, including signed ICFs, pertaining to the conduct of the study updated from 15 years to 25 years.	To align with wording in the ICF and in accordance with AstraZeneca CSP protocol template v7.0, Doc ID TMP-0010225 (dated November 2022) which is based on the TransCelerate Common Protocol Template v9.0.

Section Number and Name	Description of Change	Brief Rationale
Appendix A 9 Study and Site Start and Closure	Examples of reasons for early termination of the study by AstraZeneca were added.	To clarify the possible reasons for the early termination of the study.

Version 2.0, 30 June 2022
Version 1.0 of the protocol was not published or used; therefore, there is no history of amendments to include for version 2.0 of the protocol. Version 2.0 was the first version to be submitted to any Health Authority/Ethics committee.

Version 1.0, 05 May 2022
INITIAL CREATION

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