STATISTICAL ANALYSIS PLAN	
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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)

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
ANCA	Anti-neutrophil cytoplasm antibodies
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Chemical
ATP	According to Protocol
AWE	Acute worsening event
B	Blood
BCSS	Breathlessness, Cough and Sputum scale
BD	Bronchodilator
BDRM	Blinded data review meeting
BMI	Body Mass Index
BP	Blood pressure
BSR	Baseline Scaled Ratio
CAT	COPD Assessment Test
CI	Confidence interval
C_{max}	Maximum concentration
COPD	Chronic Obstructive Pulmonary Disease
COPDCompEx	COPD Composite Exacerbations (composite measure of chronic obstructive pulmonary disease)
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
d	Day
DBP	Diastolic Blood Pressure
DNA	Deoxyribonucleic acid

Abbreviation or Specialized Term	Definition
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic diary
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EXACT	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
gCV%	Geometric coefficient of variation
GOLD	Global Initiative for Obstructive Lung Disease
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HL	Hy's Law
hsCRP	High sensitivity C-reactive protein
IA	Interim Analysis
ICF	Informed consent form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
Ig	Immunoglobulin
IL-6	Interleukin-6
IMP	Investigational Medicinal Product
IP	Investigational Product
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
IXRS	Interactive voice/web response system
LABA	Long-acting beta-adrenoceptor agonist
LAMA	Long-acting muscarinic antagonist
LLOQ	Lower Limit Of Quantification
LSMean	Least square mean
LSMD	Least Squares Mean Difference

Abbreviation or Specialized Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MPO	Myeloperoxidase
mRNA	Messenger ribonucleic acid
NQ	Not Quantifiable
NR	Not Reportable
NS	No Sample
NT-proBNP	N-terminal pro B-type natriuretic peptide
OCS	Oral corticosteroids
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDP	Protocol Deviation Plan
PEF	Peak Expiratory Flow
PHL	Potential Hy's Law
PI	Principal investigator
PK	Pharmacokinetics
PRO	Patient reported outcome
PT	Preferred Term
QD	Quaque Die (every day)
RDMS	Regulatory Document Management System
REML	REstricted Maximum Likelihood
SAE	Serious adverse event
SS	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SD	Standard deviation
SID	Patient ID
SMQ	Standardised MedDRA Query
SoA	Schedule of Activities
SOC	System Organ Class
SoC	Standard of care
SV	Study Visit
TA	Therapeutic Area

Abbreviation or Specialized Term	Definition
TBL	Total bilirubin
TFL	Tables, Figures and Listings
T_{max}	Time to reach maximum concentration
TSH	Thyroid stimulating hormone
U	Urine
ULN	Upper limit of normal
URC	Unblinded Review Committee
VAS	Visual Analogue Scale

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	10/27/2022	Initial approved SAP	N/A	N/A
Data presentation	2/6/2023	The wording of "baseline" changed to "start of treatment" for cough frequency endpoint.	yes	Start of treatment is used in place of baseline to clarify the time of study measure.
Data presentation	2/6/2023	Text moved from Table 9 to footnotes: "**Intercurrent events are events occurring after treatment initiation (eg, premature treatment discontinuation, 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.**	yes	Clarification of intercurrent events in the study.
Secondary endpoint(s)	2/6/2023	Patient reported outcome questionnaire changed from E-RS:COPD to EXACT throughout and copy of EXACT added in Appendix G of the CSP.	yes	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.
Derivation of secondary endpoint(s)	2/6/2023	Clinical spirometry (post-BD) site measurement added at SV4.	yes	To align with other site visits.
Secondary endpoint(s)	2/6/2023	Exploratory spirometry objective and endpoints added.	yes	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 (Section 4.2.9).
Data presentation	2/6/2023	Exploratory objective and endpoints added to measure effect of sputum MPO concentration (added as subgroup analysis)	yes	To clarify intended exploratory analysis for sputum MPO concentration. This does not have a significant impact on safety and scientific value of the study.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	2/6/2023	Creation of new CSP 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.**" Updated Section 5 Interim Analysis	yes	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.
Derivation of secondary endpoint(s)	2/6/2023	AECOPD definition, start and stop dates added.	yes	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 define the start and stop dates of AECOPD.
Derivation of secondary endpoint(s)	2/6/2023	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 (Section 4.2.9).	yes	To clarify acceptable locations for study virtual spirometry assessments and to clarify the study procedure for face-to-face and virtual spirometry assessments.
Secondary endpoint(s)	2/22/2023	Daily assessments of BCSS and Cough VAS will be analysed as 2-weekly means according to periods defined in Section 3.3.3.	no	
Data presentation	12/27/2023	An administrative IA will be conducted after 136 (70% of the required 194) first COPDCompEx events have occurred	yes	To align with CSP v5.0
Data presentation	12/27/2023	Added Recurrent Rate analysis for both CompEx and Exacerbations	no	

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Derivation of secondary endpoint(s)	5/10/2024	Added visits SV4 and SV7 to make it clearer when virtual and face-to-face spirometry assessments will be performed.	yes	To clarify the visits for face-to-face and spirometry assessments.
Secondary endpoint(s)	5/10/2024	Text updated in section 4.2.3.4 to add Week 4 and Week 12 for change from baseline analysis.	yes	To be consistent across SAP.
Statistical analysis method for secondary endpoint(s)	5/10/2024	Updated to use Region will be added as a random effect	NA	To correct an error from the previous version of the SAP.
Data presentation	5/10/2024	Time at risk calculation updated. For the IA a NTF was filed	NA	In case subjects have CompEx or exacerbation from start to end of treatment
Data presentation	5/10/2024	The analysis windows for Table 4 updated	yes	To include maximum records for analysis
Data presentation	5/20/2024	Remove the entire Section 4.2.10 Tertiary/Exploratory Endpoint – Systemic Biomarkers of Cardiovascular Comorbidities and all the subsections.	yes	This is not a part of CSR as per the protocol
Data presentation	5/23/2024	Updated text in section 4.7.1.2 “Duration of exposure and total dose will be presented categorically by categories by every 28th day from Day 1 to Day 172, with 141-172 as the final category”	NA	To correct an error from the previous version of the SAP.
Data presentation	5/23/2024	Updated text in section 4.2.1.7 to clarify the estimates required for analysis	NA	To add clarity
Data presentation	5/23/2024	Updated text in section 4.2.3.7 to specify how the forest plot should be presented	NA	To add clarity
Data presentation	6/12/2024	Updated Table 10 to remove the abnormality criteria not required.	NA	To correct an error from the previous version of the SAP.

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Data presentation	6/12/2024	Removed text in section 3.3 – "This will not be part of the main analyses produced for the CSR"	Yes	To include Cough substudy outputs in CSR
Data presentation	6/17/2024	Added calculation rule for cough frequency parameters	NA	To handle log transformed values
Data presentation	9/25/2024	Safety analysis will not use estimand policy and will include all on study data	No	
Data presentation	9/25/2024	Updates in handling spirometry screening and baseline data	No	To handle missing/implausible values
Data presentation	10/3/2024	Updated compliance calculation	NA	To handle data issues

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D6582C00001 supporting the clinical study report. The reader is referred to the Clinical Study Protocol (CSP) version 5.0 and the Case report Form (CRF) for details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

- The Per-Protocol Set defined in the protocol will not be used for the analysis.
- The Cough subset will then be defined as a subset of the Full Analysis Set.
- The randomized Set is added to this analysis.
- The following biomarkers will not be delivered prior to DBL and will not be part of the CSR:
    - Sputum parameters including differential cell counts, and markers of neutrophil activation and inflammation;
    - neutrophil- related circulating biomarkers;
    - Putative biomarkers of lung tissue destruction and COPD disease progression;
    - nasal lining fluid biomarkers.
- Daily assessments of BCSS and Cough VAS will be analysed as 2-weekly means according to periods defined in Section 3.3.3.
- Laboratory safety analysis will be based on abnormality and not on treatment emergent change.
- Safety analysis will not use either the While on Treatment or Treatment policy estimand policy, and will simply include all on study data.
- Screening spirometry values will be used at Baseline if the Baseline results are missing. For % predicted FEV1 and FVC, implausible values due to data issues will be excluded from statistical analysis

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The present study is aimed to evaluate the efficacy and safety of the myeloperoxidase (MPO) inhibitor AZD4831 in the treatment of moderate to severe COPD compared to placebo.

The study will be event-driven thus the enrolment will be stopped after approximately 194 participants have had a COPDCompEx event; when the last enrolled patient completes 12 weeks of treatment, the study will stop, thus the treatment will be over a minimum 12-week and maximum 24-week period followed by 2 weeks of follow-up.

An administrative Interim Analysis (IA) will be conducted after the 136 first COPDCompEx events (70% of the required 194 events) have occurred. It will allow an early assessment of efficacy for AZD4831 according to the decision framework (Frewer et al 2016) and safety. No formal statistical test will be conducted. The IA assessment will be used to guide internal (AstraZeneca) decision-making regarding further development of the AZD4831 program. As a result, no alpha will be spent at the IA.**Analysis Populations**

The following populations are defined for the analysis:

- All Patients (Screened set)

Will include all the participants who have signed the informed consent form during the screening period and have been screened. Participants who have been randomised will be analysed according to their planned study intervention group. Participants not randomised will be summarised only in Total column.

- Randomised set

Will include all the participants who have signed the informed consent form during the screening period and have been randomised. Participants will be analysed according to their planned study intervention group.

- Full Analysis Set (FAS)

Will include all randomised participants who received at least one dose of study intervention. Participants will be analysed according to planned study intervention. Efficacy analyses will be based on the FAS.

- Safety Analysis Set (SS)

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 SS.

- PK set

Will include all participants who received AZD4831 and who have evaluable PK data for AZD4831, with no important protocol deviations thought to impact on the analysis of the PK data.

- Cough subset

Will include the subset of FAS set who consented to the cough substudy.

'All Patients' population will be used to summarise all participants disposition. The FAS population will be used to summarise all demographic and baseline characteristics, concomitant medications, and efficacy measures. The Safety set will be used to summarise all safety measures (AEs, laboratory tests, ECG, and vital signs). The PK population will be used to summarise PK measures. The Cough substudy population will be used to summarise substudy specific efficacy measures.

3.3 General Considerations

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 designed to evaluate the efficacy and safety of AZD4831 administered QD using a tablet in adult patients with confirmed moderate to severe symptomatic COPD (FEV1/FVC < 0.7, ≥ 10 pack-years smoking history, and post-BD FEV1 $\geq 25\%$ 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 with a history of pneumonia or who are otherwise deemed unsuitable for ICS). The treatment will be over a minimum 12-week and maximum 24-week period. Further details about inclusion and exclusion criteria are available in Section 5 – Study population in the CSP.

Approximately 406 participants will be randomised 1:1 to AZD4831 QD or placebo QD. The randomisation will be stratified by country. The study will be blinded to both participants and investigators/site staff as well as to the sponsor.

The entire study period is planned to take between 18 and 30 weeks for each individual patient: a 4-week screening period, minimum 12 weeks to a maximum 24 weeks of dosing and 2 weeks of follow-up. The enrolment will be stopped after approximately 194 COPDCompEx events have occurred, and when the last enrolled patient completes 12 weeks of treatment, the study will stop. At the point the study ends due to the required number of COPDCompEx events occurring, participants who are receiving study intervention between Weeks 12 and 24 at the time the last patient completes Week 12 should attend SV7 as soon as possible, continuing treatment until they do. They should then attend SV8 14 ± 3 days

later. For further details and the Schedule of Activities, refer to Table 1 – Schedule of Activities in the CSP.

Study product

The study product is AZD4831 and it will be administered orally once a day as tablet containing 5 mg of investigational product (IP). 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. No dose modification is allowed during the study.

Sample size determination

The study is powered using COPDCompEx, a composite endpoint used to estimate the magnitude of treatment effect on moderate and severe exacerbations of COPD. The time to first COPDCompEx event will be compared between AZD4831 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 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 the randomisation of 406 participants.

Cough Monitoring Substudy

A cough monitoring substudy will be performed alongside this study, where a subset of participants (maximum of 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 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 (e.g., PEF or FEV1), cough/COPD symptom scores (e.g., BCSS, CAT, and cough VAS) and sputum/blood biomarkers (e.g., MPO concentration).

3.3.1 General Study Level Definitions

3.3.1.1 Study Day and Baseline

Whenever data is summarised over time, study day will be calculated based on the actual assessment date. All data will be summarised in relation to date of first IP administration.

If actual assessment date is prior to the first IP administration, then study day will be:

Study day = Actual assessment date – first IP administration date.

If actual assessment date is on or after the first IP administration, then study day will be:

Study day = Actual assessment date – first IP administration date + 1.

In general, the last non-missing measurement prior to first application of IP will serve as the baseline measurement for efficacy and safety endpoints.

If multiple visits are equally eligible to assess patient status at baseline (for example assessments both on the same date prior to first dose of IP administration), the average (for numeric values)/worst (for categorical values) of the measurements will be taken as the baseline value. If several assessments are performed on the same day as first dose of IP administration, only those with time recorded prior to IP time of administration will be used to assess patient status at baseline (i.e. if time of assessment on the same day as IP administration is missing, the assessment will be assumed to be collected after administration).

If no value exists before the first dose of any study drug, then the baseline value will be treated as missing.

Orthostatic blood pressure measurements, even if assessed prior to IP administration, will not be used as baseline; they will be summarised and listed separately.

For daily PEF, Cough VAS Assessment and BCSS, baseline will be defined as the average from last 2 weeks (14 days) results prior to first dose of investigational product, i.e. from evening of Study Day -14 to the morning of Study Day 1. If there are fewer than 7 completed days in the 14-day baseline period (where a complete day = entry from the evening AND the following morning, i.e. one day will include all the data performed at or after 12.00 in the afternoon up to 12.00 the following morning) then baseline will be set to missing.

The baseline value of each CompEx variable will be defined as the average of all available measurements during the baseline period. There must be at least 50% of non-missing daily assessments for a variable in order for baselines to be calculated. Daily assessments could be made up of a single assessment in either the morning or evening, or two assessments daily, depending on the variable. For a baseline window of 14 days and for variables where assessments are available morning and evening, there should be at least 7 days of non-missing morning assessments and 7 days of non-missing evening assessments. For variables using once daily assessment, 7 days of non-missing assessments (from either morning or evening, depending on when the variable is captured) should be used.

The baseline cough frequency is derived from the cough monitoring performed at Visit 3 (or Revisit 3 for rescreened participants). For cough frequency, a baseline value will be defined for 24h, waking and sleeping.

For spirometry, if multiple assessments have been collected during the same day, the 'best result' flag out of all measurements per timepoint (including baseline) will be used in the analysis.

3.3.1.2 Derivations

Absolute change from baseline

Absolute change from baseline will be derived as follows:

Absolute change from baseline = (post-randomisation value – baseline value).

Time since COPD diagnosis (years)
Time from COPD first diagnosis date to randomization will be calculated as (date randomized minus date of first diagnosis of COPD plus one) divided by 365.25. If date of first diagnosis of COPD is partially missing, then imputed date will be used.

Time since COPD symptoms started (years)
Time from COPD first symptoms date to randomization will be calculated as (date randomized minus date of first symptoms of COPD plus one) divided by 365.25. If date of first symptoms of COPD is partially missing then imputed date will be used.

Time since last exacerbation (months)
Time since last COPD exacerbation date to randomization will be calculated as (date randomized minus date of most recent exacerbation plus one) divided by 365.25 and multiplied by 12. If date of first symptoms of COPD is partially missing then imputed date will be used.

Total number of COPD exacerbations within previous 24 months prior to screening
This number is derived by counting the number of events occurring prior the screening.

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.

Time from first IP administration to AE onset (days)
Time from first IP administration to AE onset will be calculated as date of AE onset minus date of first IP administration plus one.

Time from latest IP administration to AE onset (days)
Time from latest IP administration to AE onset will be calculated as date of AE onset minus date of last IP administration plus one.

Time from first IP administration to death (days)
Time from first IP administration to death will be calculated as date of death minus date of first IP administration plus one.

Time from latest IP administration to death (days)
Time from latest IP administration to death will be calculated as date of death minus date of latest IP administration plus one.

Duration of AE (days)
Duration of AE will be calculated as stop date of AE minus start date of AE plus one.

Duration of acute worsening events (days)
Duration of acute worsening events (AWE) will be calculated as stop date of AWE minus start date of AWE plus one. If two or more AWEs overlap then the duration of worsening will be calculated as stop date of latest AWE minus start date of first AWE plus one.

Duration of Interruptions
Duration of interruption will be calculated as the end date of dose interruption minus the start date of dose interruption plus one.

The start date of dose interruption is the day when drug was interrupted and the treatment was not administered.

3.3.1.3 Handling of missing data

No imputation for missing efficacy endpoints will be done.

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e., below the lower limit of quantification) will be imputed as "0.5x LLOQ" in the calculation of summary statistics but displayed as "< x" in the listings. No imputation will be done for laboratory values of the form ">x" (i.e., above the upper limit of quantification) and the value ">x" will be displayed in the listings. Note that 0 should not be used as an imputed value in case the endpoint requires a log transformation.

Additionally, adverse events (AEs) that have missing causality (after data querying) will be assumed to be causally related to study drug.

Plasma concentrations below the lower limit of quantification will be reported as NQ (Not Quantifiable) in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean, gmean ± gSD and gCV% will be set to NC (as Not Calculated). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, minimum, median and maximum will be reported as NQ and the gCV% and gmean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

3.3.1.4 Dates Imputation

Imputation of partial missing AE dates

Date and time of AE are mandatory eCRF fields. In the rare cases of missing AE date, following rules will be applied. Completely missing AE dates are not imputed.

Partial missing AE end dates are imputed as below:

- If the AE is ongoing, the end date is stated to missing.
- If the AE is not ongoing, and:
    - If only the day is missing: Assume the last day of the collected month.
    - If the month is missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed AE end date is after the end of study date, set the AE end date to end of study date.

Before proceeding with the AE start date imputation, the AE end date is imputed as described above, if necessary.

Only partial AE start dates are imputed. Dates which are completely missing are not imputed. Partial dates are imputed as described below:

- If the day is missing and:
    - If the month and year are different from the month and year of the first dose of IP, assume 01-MMM-YYYY.
    - If the month and year are the same as the first dose of IP month and year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP.
    - If the month and year are the same as the first dose of IP month and year and the end date is prior to the first dose of IP, then assume the end date.
- If the month is missing and:
    - If the year is different from the year of first dose of IP, assume 01-JAN-YYYY of the collected year.
    - If the year is the same as the first dose of IP year and the end date is on or after (including ongoing / missing) the first dose of IP, then assume the date of the first dose of IP.

- If the year is the same as the first dose of IP and the end date is prior to the first dose of IP, then assume the end date.

After applying these rules, if the imputed AE start date is after a complete AE end date then assume the same date as the complete AE end date; if the end date is missing and the imputed AE start date is after the end of study date then assume the same date as the study end date.

Imputation of partial missing medication dates

Both, completely missing and partially missing concomitant medication start dates are not imputed.

Completely missing medication end dates are not imputed. Partial missing concomitant medication end dates are imputed as below:

- If the medication is ongoing, the end date is set to missing.
- If the medication is not ongoing, and:
  - If only the day is missing: Impute with the last day of the collected month.
  - If the month is missing: Impute with 31-DEC of the collected year.

In case the medication end date is after the end of study date after applying the above rules, the concomitant medication end date should be set to end of study date.

Imputation of partial missing COPD/Medical history dates

Only partial COPD/medical history dates will be imputed. Dates which are completely missing will not be imputed. Partial start dates will be imputed as described below:

- If only day is missing, then impute the first day of the month.
- If the month is missing, then impute 1st of JAN of the collected year.

Partial end dates will be imputed as described below:

- If only day is missing, then impute the last day of the month.
- If month is missing, then impute 31st DEC of the collected year.

3.3.2 Periods

Pre-treatment period

The pre-treatment period starts at the date of signed informed consent and ends before the date and timepoint of first dose of Investigational Product (IP).

On-treatment period

The on-treatment period will be calculated from the date and timepoint (as in time of day) of the first dose of IP to the earliest of date of last dose, date of withdrawal of consent or date of death. If withdrawal of consent or death did not occur, it will be calculated from the time of the first dose of IP to the earliest of date of last dose of study drug or the last study visit. If the timepoint of first dose of IP is missing, only the day of first dose of IP will be used.

Follow-up period

The follow-up period will be calculated from the date of last dose of IP + 1 day to the date of last visit.

3.3.3 Visit Window

For COPDCompEx and the exacerbation related analyses no analysis visit windows will be applied.

For PK related analyses no analysis visit windows will be applied and the actual visits/time points will be used instead.

With the exception of the above, visit windows will be used for all scheduled assessments to allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless specified otherwise, all efficacy and safety analyses will be based on the analysis visit windows. The actual assessment day will be mapped to the planned study visit following the analysis visit windowing rules below:

- If screening and re-screening visits have same date and time then the re-screening assessment will be used in the analysis.
- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- If more than one non-missing assessment actual dates are equidistant from the target day, the earlier assessment will be used in the analysis.

Table 1 Analysis visit windows for CAT and EXACT

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -4	Screening	-28	All assessments up to and including Day -1
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1prior to the first administration of investigational product

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV5	Week 12	Week 12	84	All assessments on or after the first administration of investigational product to 127
SV7	Week 24	Week 24	168	≥128

SV = Study Visit.

Table 2 Analysis visit windows for serum chemistry, haematology, vital signs

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -4	Screening	-28	All assessments up to and including Day -1
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1 prior to the first administration of investigational product
SV4	Week 4	Week 4	28	All assessments on or after the first administration of investigational product to 56
SV5	Week 12	Week 12	84	57 to 127
SV7*	Week 24	EOT [a]	• For completed participant who performed Week 24: 168 For completed participant who performed Week 12 only: 84	• For completed participant who performed Week 24: 128 to 176 For completed participant who performed Week 12 only: 57 to 127
SV8†	End of safety period	14 days post treatment		Treatment end date + 14 (+/-3) days

[a] EOT may occur from Week 12 onwards.
Which means that the Week 12 assessment may need to be duplicated for EOT using the Penultimate Observation Carried Forward Imputation Technique, ensuring EOT assessment will also contribute to the Week 12 summary statistics

*If a subject's visit is marked with EOT it is automatically allocated to Protocol Visit SV7. If a subject's SV5 occurs after End of Enrolment, then this visit is also duplicated as SV7.
†If a subject's visit is marked as '14 days post treatment', it is automatically allocated to Protocol Visit SV8
SV = Study Visit.

For vital signs, the analysis visit will be "Day 1" for the post-dose assessment done the day of the first administration.

Table 3 Analysis visit windows for exploratory biomarkers (blood) and clinic spirometry (post-BD)

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -4	Screening	-28	All assessments up to and including Day -1
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1 prior to the first administration of investigational product
SV4	Week 4	Week 4	28	All assessments on or after the first administration of investigational product to 56
SV5	Week 12	Week 12	84	57 to 127
SV7	Week 24	Week 24	168	≥128

BD = Bronchodilator; SV = Study Visit.
For Spirometry assessment at screening, the maximum reading from each series will be used in the analysis. For subjects who have two series of Spiroload screening data, the maximum reading from the latter series will be used for analysis.

Table 4 Analysis visit windows for Thyroid test

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -4	Screening	-28	All assessments up to and including Day -1
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1 prior to the first administration of investigational product
SV5	Week 12	Week 12	84	All assessments on or after the first administration of investigational product to 127
SV7*	Week 24	EOT[a]	For completed participant who performed Week 24: 168 For completed participant who performed Week 12 only: 84	For completed participant who performed Week 24: 128 to 176 For completed participant who performed Week 12 only: all assessments on or after the first administration of investigational product to 127
SV8†	End of safety period	14 days post treatment		Treatment end date + 14 (+/-3) days

[a] EOT may occur from Week 12 onwards. Which means that the Week 12 assessment may need to be duplicated for EOT using the Penultimate Observation Carried Forward Imputation Technique, ensuring EOT assessment will also contribute to the Week 12 summary statistics

* If a subject's visit is marked with EOT it is automatically allocated to Protocol Visit SV7
† If a subject's visit is marked as '14 days post treatment', it is automatically allocated to Protocol Visit SV8
SV = Study Visit.

Table 5 Analysis visit windows for Urinalysis

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -4	Screening	-28	All assessments up to and including Day -1
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1 prior to the first administration of investigational product
SV8	End of safety period	14 days post treatment	> Date of last IP intake	All assessments after the last administration of investigational product

SV = Study Visit.

Table 6 Analysis visit windows for ECGs, Blood sample for target engagement assay, Whole blood RNA PAXgene collection form mRNA analyses, Plasma sample for proteomics, Blood sample for cell-free DNA analysis, Nasal mucosal lining fluid, Spontaneous sputum

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -4	Screening	-28	All assessments up to and including Day -1
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1 prior to the first administration of investigational product
SV5	Week 12	Week 12	84	All assessments on or after the first administration of investigational product

ECG = Electrocardiogram; SV = Study Visit.

For all other assessments (e.g., cough monitoring), there will be no analysis visit windows, the data will be reported according to CRF visit.

Table 7 Analysis visit windows for Lying and Standing (orthostatic) BP

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 1	Day 1 Pre-dose	1	All assessments on Day 1 prior to the first administration of investigational product
SV3	Week 1	Day 1 Post-dose	1	All assessments on Day 1 post the first administration of investigational product

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV5	Week 12	Week 12	84	All assessments before the administration of investigational product from Day 81-Day 87

SV = Study Visit.

Daily assessments from eDiary (PEF, BCSS, cough VAS) will primarily be summarised and analysed as 2-weekly averages, separately. The assessment period of visit windows will be defined in Table 8.

Table 8 Labelling of 2-weekly periods for daily PEF, BCSS, cough VAS

2-weekly period	Adjusted defined windows visit	Scheduled day
Baseline: as defined in Section 3.3.1.1	Baseline	1
Period 1: Evening of Day 1 – Morning of Day 15	Week 2	15
Period 2: Evening of Day 15 – Morning of Day 29	Week 4	29
Period 3: Evening of Day 29 – Morning of Day 43	Week 6	43
Period 4: Evening of Day 43 – Morning of Day 57	Week 8	57
Period 5: Evening of Day 57 – Morning of Day 71	Week 10	71
Period 6: Evening of Day 71 – Morning of Day 85	Week 12	85
Period 7: Evening of Day 85 – Morning of Day 99	Week 14	99
Period 8: Evening of Day 99 – Morning of Day 113	Week 16	113
Period 9: Evening of Day 113 – Morning of Day 127	Week 18	127
Period 10: Evening of Day 127 – Morning of Day 141	Week 20	141
Period 11: Evening of Day 141 – Morning of Day 155	Week 22	155
Period 12: Evening of Day 155 – Morning of Day 172*	Week 24	169

*the 2-weekly period for Period 12 is extended to "Morning of Day 172", to allow for the +3 day window.

The Early Discontinuation and unscheduled visits will be included when applying the visit windows to ensure that all available data are used in the analysis.

For 2-weekly summaries, the mean of all non-missing observations within an assigned window is calculated. If there are fewer than 7 completed days in the 14 day period (where a complete day = entry from the evening AND the following morning) then the analysis value will be set to missing.

3.3.4 Handling of Unscheduled Visits

Any data collected at early discontinuation and unscheduled visits will be listed and included in the definition of maximum/minimum value. The Early Discontinuation and Unscheduled visits will be included when applying the visit windows to ensure that all available data are used in the analysis.

3.3.5 Multiplicity/Multiple Comparisons

No multiplicity/multiple comparison are planned for this study.

3.3.6 Handling of Protocol Deviations in Study Analysis

The deviations from the protocol will be classified as important or non-important by blinded members of the study team.

The list of study specific IPDs is provided in the AstraZeneca Protocol Deviations Plan (PDP). Refer to the PDP for all details of IPDs. Important deviations will include the following:

- Inclusion criteria deviations
- Exclusion criteria deviations
- Discontinuation criteria for study treatment met but participant not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but participant not withdrawn from study
- Investigational product deviation
- Excluded medications taken
- Deviations to study procedure
- Other important protocol deviations

Additionally, all protocol deviations and major issues related to COVID-19 (such as missed visit, procedure not performed at visit etc.) will be captured with the prefix “COVID19” for CSR reporting.

All important protocol deviations except for dosing error will be identified and documented by the study team prior to unblinding of the trial.

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

3.4 General Principles and Analysis Methods

Efficacy analyses will be performed using the FAS. Demography and baseline characteristics will be summarised by study intervention group for the FAS. Safety analyses will be performed on SS.

Study intervention groups will be displayed as follows:

- AZD4831
- Placebo

A column reflecting all participants ("Total") will be included in tables that summarise study population data.

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, SD, median, upper and lower quartiles, minimum, and maximum. For log-transformed data geometric mean, CV%, median, minimum and maximum will be presented. Categorical variables will be summarised by frequency counts and percentages for each category.
- Concentration data will be summarised using descriptive statistics, including n, n<LLOQ, geometric mean, CV%, arithmetic mean, SD, minimum, median, and maximum values. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a log scale.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding study intervention group. Overall totals will be calculated for baseline summaries only.
- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The SD will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. CV%, where reported, will always be reported to 1 decimal place.
- PK concentration data will be presented in the listings to the same number of significant digits as the data received from the bioanalytical laboratory (usually to 3 significant figures) and against the same units as received. PK concentration descriptive statistics will all be presented to 1 additional significant figure than original data. Min, max will be presented as original data, n and n<LLOQ which will be presented as integers.
- For categorical data, percentages will be rounded to 1 decimal place.
- SAS® version 9.3 (as a minimum) will be used for all analyses.

3.4.1 Time to event analysis

Time to event endpoints will be analysed using Kaplan-Meier survival analysis (PROC LIFETEST).
The following results at Weeks 4, 12, 18 and 24 will be reported by study intervention:

- The number of participants at risk
- the number of censored participants
- the number of events
- Kaplan-Meier estimates and CI

The Kaplan-Meier curves (active versus placebo) will be compared with a two-sided logrank test stratified by region.

Time to event endpoint will be displayed graphically using a Kaplan-Meier plot.

A Cox proportional hazard model stratified by region will be fitted with study intervention as covariate. If any regions have very few events (i.e. <10) the regions can be collapsed as appropriate. The Efron approximation will be used for any tied data. The hazards proportionality assumption of the model will be examined graphically using plots of complementary log-log (event times) versus log (time). If these raise concerns, the variation in treatment effect will be described by presenting piecewise hazard ratios calculated over distinct time-periods. The HR from the primary analysis will then represent the average HR, which can be potentially misleading and should be interpreted with caution (ref: Bartlett et al, 2020). Alternative analysis methods not assuming proportional hazard could also be considered, for example landmark analysis comparing Kaplan-Meier curves at a particular time point.

The reportable results for this model will be:

- hazard ratio estimate for the study intervention
- hazard ratio two-sided CI for the study intervention
- two-sided Wald test p-value for the hazard ratio

3.4.2 Analysis of Covariance (ANCOVA)

The ANCOVA model will be used to fit change from baseline for continuous endpoints collected at only one post-baseline visit. The response variable is the value of the variable of interest at the scheduled post-baseline visit. Region will be added as a random covariate. The

study intervention will be the fixed effect with the baseline value of the variable of interest as covariate. Comparisons of AZD4831 versus placebo will be assessed. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear mixed model; two-sided difference test, with alpha level at 10% will be used to compare the difference in means and for the confidence interval calculation. No imputation will be made for missing data.

The reportable results from the model will be:

- The least-squares means (LSmeans) and their standard errors for each study intervention group;
- The difference between AZD4831 and placebo (LSmeans difference) together with its two-sided 90% CI;
- The two-sided p-value for the difference between AZD4831 and placebo.

3.4.3 Mixed Model Repeated Measures (MMRM)

The MMRM model will be used to fit change from baseline for continuous endpoints that have data at several post-baseline visits. The model will include all available data from all visits, irrespective of whether the patient discontinued study intervention. Since a repeated measures model is being applied, no imputation will be made for missing data. Region will be added as a random effect. The model will include fixed effects for baseline, visit, study intervention and the baseline by visit and study intervention by visit interactions. An unstructured covariance matrix will be used to describe the correlations on a patient between visits, and the Kenward-Roger correction will be used for degree of freedom approximation in the generation of the model. In the event that the model with unstructured covariance matrix fails to converge, an alternative such as autoregressive or compound symmetry will be used instead. Estimates of the least square (LS) mean change from baseline for each study intervention, and the difference between them (AZD4831-placebo), together with two-sided 90% CI, will be obtained from the model for each visit. The study intervention effect will be tested at the 10% two-sided level of significance.

The reportable results from the model are:

- The LSmeans change from baseline at each visit and their standard errors for each study intervention group.
- The difference in change from baseline at each visit between AZD4831 and placebo (LSmeans difference) together with its two-sided 90% confidence interval (CI).
- The two-sided p-value for the difference in change from baseline at each visit between AZD4831 and placebo.

3.4.4 Negative binomial regression

Negative binomial regression will be used for the analysis of event rates. In this study the response variable in the model will be either the number of COPDCompEx event or the number of moderate or severe AECOPD exacerbations experienced by a participant. The model will include study intervention group as a fixed effect and logarithm of the participant's corresponding 'at risk' time will be used as an offset variable in the model to adjust for participants having different exposure times during which the events occur. All available data from participants will be included, irrespective of whether they discontinued study intervention.

The model will include study intervention group and geographical region as fixed effects.

The standard parameterization approach (NB2) of the negative binomial model will be applied using PROC GENMOD (SAS procedure).

The estimated annual event rate (AER) for each treatment, the treatment effect (ie, the rate ratio of actual study intervention group versus placebo), corresponding two-sided 90% CI, and two-sided p-value for the rate ratio will be presented. The estimate of the negative binomial overdispersion parameter will also be reported.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers patient disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication and study drug compliance.

4.1.1 Patient Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants screened are those who were enrolled, i.e., participants who agreed/whose legally acceptable representatives agreed to participate in a clinical study following completion of the informed consent process.

Screening failures/participants not randomised are those potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned in the study. 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.

Participants randomized are defined in Section 3.2.

Participants started treatment are all randomised participants who reported at least one administration of the study drug.

Participants completed treatment are participants who completed at least 12 weeks of treatment. Participants who are receiving study intervention between Weeks 12 and 24 at the time the last patient completes Week 12 should attend Study Visit (SV)7 as soon as possible, continuing treatment until they do. They should then attend SV8 14 ± 3 days later.

Participants discontinued treatment are participants who did not complete 12 weeks of treatment due to a permanent discontinuation of the study drug administration.

4.1.1.2 Presentation

Patient dispositions (number and percentage) of subjects enrolled, subjects not randomised (incl. reasons), subjects randomised, subjects randomised and who did not receive treatment, subjects who started treatment, subjects who completed the treatment, subjects who discontinued treatment (incl. reasons), subjects included in the cough substudy, subjects who completed the study and subjects withdrawn from study (incl. reasons) will be presented in a summary table for each study intervention group and overall. A listing including all standardised disposition terms will also be provided for all discontinued subjects and subjects completing the study. Both the table and the listings will be based on the screened set.

To demonstrate balance in stratification factor categories (i.e. countries), the number and percentage of participants in each category will be summarised by study intervention group and overall focusing on the randomised set.

The recruitment per country and site will be provided based on the screened set, while the global/country situation study disruption will be summarised on the full analysis set.

The number and percentage of participants with one or more disruption due to COVID-19 pandemic will be presented by study intervention group considering the participants valid for the full analysis set. A listing of all the participants affected by COVID-19 related study disruption will be produced by unique patient number identifier, investigational site, and a description of how the individual's participation was altered. COVID-19 related study disruptions can be:

- Visit related (if visit is impacted by global/country situation, then contact mode will be specified);
- Study drug related (if study drug action taken (except "Drug Withdrawn") was impacted by global/country situation; study drug administration or location was impacted by global/country situation; who performed a study drug administration);

- Discontinuation of study drug due to COVID-19 pandemic (if study drug action taken "Drug Withdrawn" was impacted by global/country situation);

- Withdrawal from study (if primary reason for ending study is related to global/country situation).

Randomisation scheme and codes as well as participants receiving the various batch of investigational product will also be listed for all randomised participants.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis populations used in the analysis have been described in Section 3.2.

4.1.2.2 Presentation

The number of participants belonging to each analysis population will be presented in a summary table for each study intervention group on the Screened set.

A listing of all participants excluded from any population will also be provided. The listing will include reason for exclusion from respective population and will be based on the screened set.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The definition of IPD is available in Section 3.3.6. Deviations from the protocol will be assessed as important or non-important by blinded members of the study team before database hard lock and unblinding. A blind data review meeting will be held.

4.1.3.2 Presentation

The number and percentage of participants with at least one IPD, including COVID-19 related IPD, will be summarised following the PDP categories, for each study intervention group and overall.

All IPDs will also be listed for all participants included in the FAS population. All issues reported due to COVID-19 pandemic, regardless of whether the type of issue is considered a protocol deviation or not, will be listed separately.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics are collected pre-treatment as per schedule of activities (CSP Section 1.3). they include age, age group (≥ 40 – < 65; ≥ 65 - ≤ 80), sex, race, ethnic group, region and country. Age is the age at screening as reported in the eCRF.

4.1.4.2 Presentation

All demographics will be presented in summary tables for each study intervention group and overall. Age will be described as a continuous variable; all the other demographics (i.e., age group, gender, race, and ethnicity) will be summarised as categorical variables with the number and percentage of participants by categories.

All demographics will also be provided in listings.

The tables and the listings will be based on the FAS.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Patient characteristics are collected pre-treatment as per schedule of activities (CSP Section 1.3). They include height (cm) and weight (kg) at baseline.

Body Mass Index (BMI) (kg/m²) is calculated at baseline from the height (m) and weight (kg) as follows: BMI = weight / (height^2). Only the baseline measurement for height, weight and BMI will be considered.

The lung function variables from spirometry collected at baseline/screening are: absolute and % predicted (as applicable) PEF, FEV1, FVC, FEV1/FVC, forced mid-expiratory flow (FEF25-75%), and forced inspiratory vital capacity. Screening spirometry data will be used for any subjects with missing baseline spirometry data.

For patients with missing Baseline spirometry results, screening results will be used, with ZephyrX results prioritised over Unify if both are available.

In case data issues for % predicted FEV1 and FVC are not resolved for database lock, any implausible values (i.e. <1% or >500%) will be set to missing, and consequently excluded from analysis.

4.1.5.2 Presentation

All patient-specific characteristics will be presented in summary tables for each study intervention group and overall. Height, weight, and BMI will be summarised as a continuous variable. BMI categories (<18, ≥ 18 to < 25, ≥ 25 to < 30, ≥ 30 (kg/m²) will be summarised as a categorical variable.

Lung function parameters will be summarised in a separate table as continuous variables.

Lung function parameters (FEV1, FVC, FEV1/FVC and FEV1% predicted) at screening will be summarised in a separate table as continuous variables.

All patient-specific characteristics will also be provided in listings.

The tables and the listings will be based on the FAS population.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The patient's COPD history will be collected and will include questions related to the:

- COPD first diagnosed date
- First appearance of COPD symptoms date
- GOLD Classification
- Occurrence of previous admission to ICU for COPD in past 24 months
- Required mechanical ventilation for COPD
- Occurrence of Cough at least several days/week over past 3 months

Brought up phlegm at least several days/week over past 3 months

4.1.6.2 Presentation

The following variables will be summarised by intervention group and overall for FAS:

- Time since COPD diagnosis (years)
- Time COPD symptoms started (years)
- GOLD Classification
- Occurrence of previous admission to ICU for COPD in past 24 months
- Number of moderate and severe exacerbation within 24 months prior enrolment
- Frequent productive cough
- Use of disease-related medications (ICS + LABA + LAMA or ICS + LABA or LABA + LAMA)

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Complete medical and surgical history will be collected as per SoA (CSP Section 1.3). Medical history will be coded in Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher.

4.1.7.2 Presentation

Medical history will be presented in summary tables as number and percentage of participants by System Organ Class (SOC) and Preferred Term (PT) for each study intervention group and overall. Participants with multiple events in the same SOC/PT will be counted only once

in that SOC/PT. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted alphabetically by SOC and PT. The tables will be based on the FAS population.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Any prior and concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The WHO-DD March 2022 B3 Global or higher will be used to classify medications by WHO ATC classification of ingredients. The imputation method described in Section 3.3.1.4 will be used in case of medication stop date partially missing. Completely missing stop date will not be imputed. Completely missing or partially missing concomitant medication start dates will not be imputed.

After the end date imputation, the medications will be classified as either prior or concomitant (but not both) according to its stop date:

- Prior medication is defined as any medication with a stop date prior to the first dose of IP (exclusive).

- Concomitant medication is defined as any medication with a stop date on or after the first dose of study drug, or any medication taken prior to study drug and that is ongoing.
  Medications with completely missing stop date are classified as concomitant.

Disallowed medications will include medications defined as prohibited according to CSP Section 6.5. They will be defined following a physician review (prior to database lock) of the unique combinations of ATC code classifications and generic terms captured and detailed in the Integrated Data Review Plan.

COVID-19 vaccine information will be recorded and summarised as part of concomitant medication. For reporting purposes, COVID-19 vaccines will be selected using ATC code J07BX.

4.1.8.2 Presentation

The number and percentage of participants receiving prior or concomitant medication (by ATC4 classification system codes and generic name) will be presented by study intervention in separate tables for the FAS population. The number and percentage of participants receiving prior disease related medication will be presented by study intervention group for the FAS population by study intervention.

A separate table will be presented for participants who take restricted prior or concomitant medications. The numbers and percentages will be calculated relative to the number of participants in the FAS population by intervention group and overall.

All medications will also be listed by patient for the FAS population.

4.1.9 Substance usage – Inhaled Tobacco

4.1.9.1 Definitions and Derivations

Smoking status (cigarettes, cigars, pipes, smokeless tobacco and electronic nicotine delivery systems) together with the consumption of cigarettes in pack-years will be collected.

4.1.9.2 Presentation

All substance usage will be presented in summary tables for each study intervention group and overall. Smoking amount consumed in pack-years will be summarised descriptively as a continuous variable; all the other substance usage variables (i.e., substance type, substance usage) will be summarised as categorical variables with the number and percentage of participants by categories.

All substance usage will also be provided in listings.

The tables and the listings will be based on the FAS population.

4.1.10 Study Drug Compliance

4.1.10.1 Definitions and Derivations

Compliance with investigational product (IP) will be calculated using the following equation:

$$IP\ Compliance\ (\%) = \frac{Number\ of\ doses\ taken}{Number\ of\ intended\ doses}\ x\ 100$$

The number of intended doses is equal to one tablet per day throughout the duration of the study for each patient, and thus it is approximated by treatment start date minus treatment end date + 1, i.e. independent of any dose interruptions.

The number of doses taken is the "actual exposure" from section 4.7.1.1, i.e. the difference between dispensed and returned tablets as recorded in eCRF. If any 'Amount Returned' field in the Drug Accountability CRF page is blank, then the Number of Doses taken – and therefore IP Compliance – is not calculated.

Participants' IP compliance will be categorized in <80%, from 80% (included) to 120% (included), >120%. Participants having IP compliance between 80% to 120% inclusive will be defined as treatment compliant.

4.1.10.2 Presentation

The compliance with IP will be presented in a summary table for each study intervention group and overall.

The number and percentage of participants by each compliance category will also be provided.

The tables will be based on the FAS population.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

All endpoint analyses will include data reported up to end of treatment (EOT) visit.

Table 9 Analyses of primary, secondary and tertiary/exploratory endpoints

Objectives	Estimand description / Outcome Measure	Population
Primary		
To evaluate the effect of AZD4831 as compared to placebo on the time to first COPDCompEx event in participants with moderate to severe COPD.	**Endpoint:** time to first COPDCompEx event. **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** Primary estimand: while on treatment. Supportive estimand: treatment policy.	FAS
Secondary		
To assess the PK of AZD4831 in participants with moderate to severe COPD.	**Endpoint:** plasma 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.	PK set

Objectives	Estimand description / Outcome Measure	Population
To evaluate the effect of AZD4831 as compared to placebo on the time to first moderate or severe COPD exacerbation.	**Endpoint:** time to first COPD exacerbation event[a] **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** while on treatment.	FAS
To assess the effects of AZD4831 as compared to placebo on post-BD FEV1 in participants with moderate to severe COPD.	**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.	FAS
To assess the effect of AZD4831 compared with placebo on respiratory symptoms in participants with moderate to severe COPD.	**Endpoint:** change from baseline in EXACT, BCSS average score, and Cough VAS average score at Week 12 and Week 24. **Population level-summary measure:** the difference in mean. **Strategy for intercurrent events:** while on treatment.	FAS
To assess the effect of AZD4831 compared with placebo on disease impact in participants with moderate to severe COPD.	**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.	FAS
Safety		
To assess the safety and tolerability of AZD4831 compared with placebo in participants with moderate to severe COPD.	**Endpoint:** safety and tolerability evaluations using AEs, SAEs, AESIs (skin reactions, including maculopapular rash, and serious infections, including pneumonia), vital sign measures, clinical	SS

Objectives	Estimand description / Outcome Measure	Population
	laboratory assessments (clinical chemistry, haematology, and urinalysis), and ECG. **Population level-summary measure:** descriptive statistics eg, absolute counts and frequencies.	
Tertiary/Exploratory		
To assess the effect of AZD4831 compared with placebo on biomarkers related to COPD disease activity.	Systemic biomarkers of cardiovascular comorbidities - including fibrinogen, hsCRP, IL-6, and NT-proBNP.	FAS
To assess the effects of AZD4831 as compared to placebo on MPO activity and concentration in sputum samples from participants with moderate to severe COPD.	Average change from baseline to Week 12 in MPO activity normalised to MPO concentration in sputum.	FAS
To assess the effects of AZD4831 as compared to placebo on spirometry endpoints measured face-to-face in participants 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.	FAS
To assess the effect of sputum MPO concentration at baseline on primary and secondary endpoints in participants 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.	FAS
To assess the effects of AZD4831 compared to placebo on change in cough frequency measured over a	Change from start of treatment in average 24-hour, waking, and sleeping cough frequency, using the VitaloJAK® Cough Monitor device, at Week 12.	Cough subset

Objectives	Estimand description / Outcome Measure	Population
24-hour period between start of treatment and 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 blood biomarkers (eg, MPO concentration).	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.	Cough subset
To assess the effects of AZD4831 as compared to placebo on COPDCompEx in participants with moderate to severe COPD.	Annualised rate of COPDCompEx events, based on the period from baseline to the last dose **Strategy for intercurrent events:** while on treatment.	FAS
To assess the effect of AZD4831 compared with placebo on moderate to severe COPD exacerbation.	Annualised rate of moderate or severe COPD exacerbations based on the period during the intervention from baseline to the last dose **Strategy for intercurrent events:** while on treatment.	FAS

[a] 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.
- Results in death.

Intercurrent events are events occurring after treatment initiation (eg, premature treatment discontinuation, 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 Premature treatment discontinuation (with the following reasons: SAE, death not due to exacerbation, COVID-19, pneumonia, other).
2 Prohibited medication.

4.2.1 Primary Endpoint – Time to First COPDCompEx Event

4.2.1.1 Definition

The COPDCompEx is a composite endpoint developed to estimate the magnitude of treatment effect on COPD exacerbations over 52 weeks, in a 12-week study. It incorporates change in symptoms, reliever use and PEF obtained from daily diary, with confirmed exacerbations and/or study drop-outs.

The definition of the event is one of the following criteria:

- *Moderate or severe exacerbations*: episodes leading to one or more of the following: hospitalization, emergency room visit, an episode of pneumonia, treatment with OCS or corticosteroid depot 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*: early treatment discontinuation due to lack of efficacy.

The COPDCompEx definition and derivation are detailed in AZ Business Rules.

Time to first COPDCompEx event is defined as time elapsed from the start of study treatment to the occurrence of the first COPDCompEx event.

4.2.1.2 Derivations

Time to first COPDCompEx event will be calculated as:

Time to first COPDCompEx event (days) = [Start date of first event/censoring – date of the first dose of study intervention+ 1].

For participants who do not experience an on-treatment COPDCompEx event, date of censoring will be the last dose date or last date of eDiary recording – whichever is earlier.

4.2.1.3 Handling of Dropouts and Missing Data

The “while on treatment” strategy will be used for the primary estimand: if an intercurrent event occurs before first COPDCompEx event, the patient will be censored at the time of intercurrent event.

For participants who do not experience an on-treatment COPDCompEx event,

- If intercurrent event is earlier than date of last dose or the last eDiary date, the participant will be censored at intercurrent event date.

- If the intercurrent event is after the last eDiary date, but earlier than date of last dose, participants who do not experience an on-treatment COPDCompEx event, date of censoring will be last day of eDiary recording.

Intercurrent events are events occurring after treatment initiation (eg, premature treatment discontinuation, 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.

4.2.1.4 Primary Analysis of Primary Endpoint

Kaplan-Meier curves, region-stratified logrank test and region stratified Cox proportional hazard (PH) model results, will be provided for time to first COPDCompEx event as specified in Section 3.4.1.

The evidence of efficacy requires a two-sided region-stratified logrank test p-value ≤ 0.10.

Kaplan-Meier curve estimates will be provided with a 90% CI.

Survival probabilities will be presented as survival curves estimated using the Kaplan-Meier method.

Diagnostic plot (log-log) will be presented to assess proportional hazard assumption.

The hazard ratio estimate from the Cox PH model will be provided with a 90% CI.

COPDCompEx data will be listed.

The analyses will be focused on the FAS population, including only those subjects with post-baseline eDiary data.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

Not applicable.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The analysis described above (Section 4.2.1.4) will be repeated applying the “treatment policy” estimand strategy as supportive. The events that occurred after intercurrent events will not be censored (i.e. will be treated as events). The treatment policy strategy used to estimate the efficacy of AZD4831 in ‘real-world’ conditions.

4.2.1.7 Subgroup Analyses

The subgroup analysis will be conducted for exploratory purposes.

The Cox proportional hazards model specified above would also be run separately with the "while on treatment" strategy for the following subgroups:

- Frequent Productive Cough (Yes; No)
- Gender (Male; Female)
- Age (≥40 – <65; ≥65 - ≤80)
- Race (as collected in CRF)
- BMI (<18; ≥18 to <25; ≥25 to <30; ≥30)
- Geographic region (North America (Canada, United States of America), Eastern Europe (Bulgaria, Poland, Turkey), Western Europe (Denmark, Germany, Italy, Netherlands, Spain, United Kingdom), Rest of the world (Argentina, Mexico, South Africa).
- Baseline FEV1 as percent of predicted (<50%; ≥50%)
- Maintenance medications:
    - ICS; no ICS
    - LABA/ICS; LABA/LAMA/ICS; LABA/LAMA
- Number of COPD exacerbations in last 24 months (<2; ≥2)
- Type of site of recruitment (primary care site; specialist care site)
- Smoking status (Current smokers; Ex-smokers)
- MPO concentration at baseline (upper tertile; middle tertile; lower tertile)

The hazard ratio estimate from the Cox PH model will be provided with a 90% CI only for subgroup categories that contain at least 20% of the total participants.

4.2.2 Secondary Endpoint – Time to First Moderate or Severe COPD Exacerbation Event

4.2.2.1 Definition

A moderate or severe AECOPD may 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 hospitalization 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.

The start and stop of a moderate or severe exacerbation is defined as:

- The start date of systemic corticosteroids or antibiotic treatment or hospital/emergency admission, whichever occurs earlier, and the stop date is defined as the last day of systemic corticosteroids or antibiotic treatment or hospital/emergency discharge, whichever occurs later.
- A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids. The corresponding stop date for this treatment will consequently be determined as the date of administration plus 2 days.
- If multiple treatments are prescribed for the same exacerbation, the earliest start date and the latest stop date will be used.

For a severe COPD exacerbation with no documented corticosteroid or antibiotics treatment, hospitalization admission/discharge dates, or emergency visit date will be used as start/stop dates

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 hospitalization or death.

A COPD exacerbation will be considered **severe** if it results in hospitalization (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.

Time to first moderate or severe COPD exacerbation event is defined as time elapsed from the start of study treatment to the occurrence of the first moderate or severe COPD exacerbation event.

4.2.2.2 Derivations

Time to first moderate or severe COPD exacerbation event will be calculated as:

Time to first moderate or severe COPD exacerbation event (days) = [Start date of first event/censoring – date of the first dose of study intervention+ 1].

The date of first moderate or severe COPD exacerbation event will be the first start date of a moderate or severe COPD exacerbation event, i.e. the earliest of the exacerbation which meets the definition of moderate or severe COPD exacerbation.

For participants who do not experience an on-treatment moderate or severe COPD exacerbation event, date of censoring will be the date of last dose.

4.2.2.3 Handling of Dropouts and Missing Data

The "while on treatment" strategy will be used: if an intercurrent event occurs before first moderate or severe exacerbation, the patient will be censored at the time of intercurrent event.

For participants who do not experience an on-treatment moderate or severe COPD exacerbation event,

- If intercurrent event is earlier than date of last dose, the participant will be censored at intercurrent event date.

4.2.2.4 Primary Analysis of Secondary Endpoint

Kaplan-Meier curves, region-stratified logrank test and region stratified Cox proportional hazard model results, will be provided for time to first moderate or severe exacerbation as specified in Section 3.4.1.

A two-sided region-stratified logrank test p-value ≤ 0.10 is required to provide evidence of efficacy. Kaplan-Meier curve estimates will be provided with a 90% CI.

Survival probabilities will be presented as survival curves estimated using the Kaplan-Meier method.

Diagnostic plot (log-log) will be presented to assess proportional hazard assumption.

The hazard ratio estimate from the Cox PH model will be provided with a 90% CI.

Exacerbations data will be listed.

The analysis will be focused on the FAS population.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.2.7 Subgroup Analyses

Not Applicable.

4.2.3 Secondary Endpoint – post-BD FEV1

4.2.3.1 Definition

All spirometry will be performed post-BD, which includes the patient's regular triple or dual (ICS + LABA or LAMA + LABA) therapy. Data collected will include absolute and % predicted (as applicable) PEF, FEV1, FVC, FEV1/FVC, forced mid-expiratory flow (FEF25-75%), and forced inspiratory vital capacity. At SV3, SV4, SV5 and SV7, face-to-face (clinic) spirometry will be undertaken at the site. Face-to-face spirometry will take the form of supervised, coached measurement by a trained healthcare professional performed in person at the site. Only measurements obtained by face-to-face spirometry will be utilized for the secondary outcome of post-BD FEV1.

For daily spirometry, if multiple assessments have been collected during the same day, the maximum value out of all measurements per timepoint (including baseline) will be used in the analysis.

4.2.3.2 Derivations

Change from baseline in post-BD FEV1 to Weeks 4, 12 and 24 will be calculated as specified in Section 3.3.1.2.

4.2.3.3 Handling of Dropouts

The 'while-on treatment' strategy will be used: which means that if an intercurrent event occurs all subsequent data for that participant are excluded from the evaluation.

4.2.3.4 Primary Analysis of Secondary Endpoint

Observed values and absolute change from baseline up to Weeks 4, 12 and 24 in post-BD FEV1 will be summarised by each intervention group for the FAS population.

Change from baseline to Week 4, Week 12 and Week 24 in post-BD FEV1 for participants with moderate to severe COPD will be analysed using MMRM as described in Section 3.4.3.

The analysis will be focused on the FAS population.

4.2.3.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.3.6 Supplementary Analyses of the Secondary Endpoint

The analysis described above (Section 4.2.3.4) will be repeated applying the "treatment policy" estimand strategy as supportive. This means if an intercurrent event occurs all subsequent data for that participant up to last dose are included in the evaluation.

4.2.3.7 Subgroup Analyses

The subgroup analysis will be conducted for exploratory purposes.

For subgroup categories that contain at least 20% of the total participants a single forest plot including all subgroups will display graphically the mean difference (AZD4831 - Placebo) in change from baseline in post-BD FEV1 at Week 12, together with the two-sided 90% CI and reference line at zero. In addition, the following statistical parameters will be displayed: total number of subjects, mean change from baseline and its standard error for each study intervention, as well as the mean difference (AZD4831 - Placebo) from baseline, together with the two-sided 90% CI.

For subgroup categories that contain less than 20% of the total participants, only the total number of subjects in each arm will be presented.

Following are the subgroups:

- Frequent Productive Cough (Yes; No)
- Gender (Male; Female)
- Age (≥40 – <65; ≥65 - ≤80)
- Race (as collected in CRF)
- BMI (<18; ≥18 to <25; ≥25 to <30; ≥30)
- Geographic region (North America (Canada, United States of America), Eastern Europe (Bulgaria, Poland, Turkey), Western Europe (Denmark, Germany, Italy, Netherlands, Spain, United Kingdom), Rest of the world (Argentina, Mexico, South Africa))
- Baseline FEV1 as percent of predicted (<50%; ≥50%)
- Maintenance medications:

- ICS; no ICS
- LABA/ICS; LABA/LAMA/ICS; LABA/LAMA

- Number of COPD exacerbations in last 24 months (<2; ≥2)
- Type of site of recruitment (primary care site; specialist care site)
- Smoking status (Current smokers; Ex-smokers)
- MPO concentration at baseline (upper tertile; middle tertile; lower tertile)

4.2.4 Secondary Endpoint – EXACT score

4.2.4.1 Definition

The exacerbations of chronic pulmonary disease tool (EXACT) is a PRO measure designed to standardize the method for evaluating the frequency, severity, and duration of both reported and unreported acute exacerbations of COPD and chronic bronchitis in clinical trials.

The EXACT total score is computed across 14 items and has a theoretical range of 0 to 100, with higher values indicating a more severe condition. Additional information regarding the patient´s condition can be obtained through 3 domain scores embedded in the measure: Breathlessness, Cough & Sputum, and Chest Symptoms. These scores also range from 0 to 100, with higher scores indicating more severe symptoms. The EXACT will be performed at on-site visits using the e-Diary.

4.2.4.2 Derivations

The derivation of the EXACT total and 3 domain scores can be found in EXACT user manual v8.0. Change from baseline in EXACT total and domains scores to Weeks 12 and 24 will be calculated as specified in Section 3.3.1.2.

4.2.4.3 Handling of Dropouts

The 'while-on treatment' strategy will be used: which means that if an intercurrent event occurs all subsequent data for that participant are excluded from the evaluation.

4.2.4.4 Primary Analysis of Secondary Endpoint

Observed values and absolute change from baseline up to Weeks 12 and 24 in EXACT total and domain scores will be summarised by each intervention group for the FAS population.

Change from baseline to Weeks 12 and 24 in EXACT (total and domain scores) will be analysed using MMRM as described in Section 3.4.3.

LSMean change from baseline and two-sided 90% CI up to Weeks 12 and 24 in EXACT total and domain scores will be presented in figures. For primary analysis, LSMean change from baseline through Weeks 12 and 24 in EXACT total and domain scores will be presented.

A listing including results from each of the domain and the total EXACT score will be produced for the FAS population.

4.2.4.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable

4.2.4.6 Supplementary Analyses of the Secondary Endpoint

Not applicable

4.2.4.7 Subgroup Analyses

Not Applicable

4.2.5 Secondary Endpoint – BCSS score

4.2.5.1 Definition

Breathlessness, Cough and Sputum Scale (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). 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. If there are repeated measurements in a day (evening), then the first measurement will be used in the analysis.

4.2.5.2 Derivations

Change from baseline in BCSS average score to Weeks 12 and 24 will be calculated as specified in Section 3.3.1.2.

4.2.5.3 Handling of Dropouts

The 'while-on treatment' strategy will be used: which means that if an intercurrent event occurs all subsequent data for that participant are excluded from the evaluation.

4.2.5.4 Primary Analysis of Secondary Endpoint

Observed values and absolute change from baseline to Weeks 12 and 24 in BCSS average total and domain scores will be summarised by each intervention group for the FAS population.

Change from baseline to Weeks 12 and 24 in BCSS average total and domain scores will be analysed using MMRM as described in Section 3.4.3.

LSMean change from baseline and two-sided 90% CI up to Weeks 12 and 24 in BCSS average total and domain scores will be presented in figures. For primary analysis, LSMean

change from baseline through Weeks 12 and 24 in BCSS average domain and total scores will be presented.

A listing including results from each of the domain and the total BCSS average score will be produced for the FAS population.

4.2.5.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.5.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.5.7 Subgroup Analyses

Not Applicable

4.2.6 Secondary Endpoint – Cough VAS

4.2.6.1 Definition

Participants will be asked to complete a cough severity VAS (100-point linear scale marked with a horizontal or vertical line by the patient, with 0 representing “no cough” and 100 representing “worst cough”) measuring subjective assessment by the patient of the prior 24 hours for severity of cough symptoms.

The Cough VAS will be completed each morning in the e-Diary until Week 24.

4.2.6.2 Derivations

Change from baseline in Cough VAS average score to Weeks 12 and 24 will be calculated as specified in Section 3.3.1.2.

4.2.6.3 Handling of Dropouts

The 'while-on treatment' strategy will be used: which means that if an intercurrent event occurs all subsequent data for that participant are excluded from the evaluation.

4.2.6.4 Primary Analysis of Secondary Endpoint

Observed values and absolute change from baseline up to Weeks 12 and 24 in Cough VAS average score will be summarised by each intervention group for the FAS population.

Change from baseline to Weeks 12 and 24 in Cough VAS average score will be analysed using a MMRM as described in Section 3.4.3.

LSMean change from baseline and two-sided 90% CI up to Weeks 12 and 24 in Cough VAS average scores will be presented in figures. For primary analysis, LSMean change from baseline through Weeks 12 and 24 in Cough VAS average score will be presented.

A listing including results from the Cough VAS average score will be produced for the FAS population.

4.2.6.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.6.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.6.7 Subgroup Analyses

Not Applicable.

4.2.7 Secondary Endpoint – Total CAT measured in clinic

4.2.7.1 Definition

COPD Assessment Test (CAT) is designed to measure how COPD impacts on a patient's daily life and how this might change over time. It consists of 8 questions that ask the patient 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.

4.2.7.2 Derivations

Change from baseline in total CAT score to Week 12 and Week 24 will be calculated as specified in Section 3.3.1.2.

4.2.7.3 Handling of Dropouts

The 'while-on treatment' strategy will be used: which means that if an intercurrent event occurs all subsequent data for that participant are excluded from the evaluation.

4.2.7.4 Primary Analysis of Secondary Endpoint

Observed values and absolute change from baseline up to Weeks 12 and Week 24 in CAT score will be summarised by each intervention group for the FAS population.

Change from baseline through Weeks 12 and 24 in total CAT score will be analysed using MMRM (see details in Section 3.4.3).

LSMean change from baseline and two-sided 90% CI for Weeks 12 and 24 in total CAT score will be presented in figure.

The number and percentage of participants with a change from baseline of -2 or less will be summarised by intervention group.

The total CAT score will be listed by patient for the FAS population.

The analysis will be focused on the FAS population.

4.2.7.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable

4.2.7.6 Supplementary Analyses of the Secondary Endpoint

Not applicable

4.2.7.7 Subgroup Analyses

Not Applicable

4.2.8 Tertiary/Exploratory Endpoint – Cough frequency

4.2.8.1 Definition

The assessment of 24-hour coughs per hour (i.e., average hourly cough frequency based on 24-hour sound recordings) will be evaluated at Visit SV3 (start of treatment) and Visit SV5 (after 12 weeks of treatment) using the VitaloJAK® Cough Monitor device for a subset of participants (up to approximately 50 participants from each arm) from selected sites enrolled in the cough substudy. 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 baseline is unsuccessful, the Week 12 recording can be omitted.

More details about VitaloJAK® Cough Monitor device can be found in the Objective Cough Endpoint documentation.

4.2.8.2 Derivations

Change from start of treatment in cough frequency to Week 12 will be expressed as baseline scale ratio (BSR) due to the log-normality of the data.

$$BSR = \exp\left(\ln Post\ Baseline - \ln Baseline\right)$$

4.2.8.3 Handling of Dropouts

Participants who drop out study early or had intercurrent events will be included for analysis using treatment policy strategy.

Treatment policy strategy means if an intercurrent event occurs all subsequent data for that participant up to last dose are included in the evaluation.

4.2.8.4 Primary Analysis of Tertiary/Exploratory Endpoint

Observed values and BSR cough frequency will be summarised with the statistics planned for log-normal data for 24h, waking and sleeping. For cough frequency parameters (24-hour, waking and sleeping) the values will be log-transformed (to base e) after adding an offset of 0.005 to bring all data above zero.

BSR cough frequency at Week 12 will be analysed using ANCOVA model for 24-hour, waking and sleeping. The response variable will be the ln(BSR cough frequency) at Week 12 with study intervention as factor for comparison of AZD4831 and placebo, ln(baseline value) as a covariate, and region will be added as a random covariate.

The reportable results from the ANCOVA are the ones described in Section 3.4.2, by back-transforming all the results (i.e. LSMean, CI), except the p-value.

Distributions of 24-hour, waking and sleeping cough frequency at baseline and Week 12 will be displayed by study intervention group with box-plots.

The average 24-hour, waking and sleeping cough frequency will also be listed by patient.

All these analyses will be based on the cough subset population.

4.2.8.5 Sensitivity Analyses of the Tertiary/Exploratory Endpoint

Not applicable

4.2.8.6 Supplementary Analyses of the Tertiary/Exploratory Endpoint

Not applicable

4.2.8.7 Subgroup Analyses

Not Applicable

4.2.9 Tertiary/Exploratory Endpoint – Change from baseline in spirometry endpoints measured face to face

4.2.9.1 Definition

Data collected will include, but are not limited to, absolute and % predicted (as applicable) PEF, FEV1, FVC, FEV1/FVC, forced mid-expiratory flow (FEF25-75%), and inspiratory capacity. The following parameters will be included in the analysis PEF, FEV1, FVC, FEV1 and FVC % predicted, FEV1/FVC, forced mid-expiratory flow (FEF25-75%) and forced inspiratory vital capacity. At SV3 and SV5, face-to-face spirometry will be undertaken at the site, followed by virtual spirometry. At SV4 and SV7, virtual spirometry will be performed away from the study site prior to attendance at the site and then face-to-face spirometry will be performed subsequently once the participant has attended the site.

4.2.9.2 Derivations

Change from baseline in spirometry endpoints to Weeks 4, 12 and 24 will be calculated as specified in Section 3.3.1.2.

4.2.9.3 Handling of Dropouts

Participants who had intercurrent events will be included for analysis using "treatment policy" strategy.

4.2.9.4 Primary Analysis of Tertiary/Exploratory Endpoint

Observed values and absolute change from baseline up to Weeks 4, 12 and 24 in spirometry endpoints will be summarised by each intervention group for the FAS population.

Change from baseline through Week 24 in spirometry endpoints for participants with moderate to severe COPD will be analysed using MMRM as described in Section 3.4.3.

Spirometry endpoints measured face to face will be summarised.

Spirometry assessments measured face to face will be listed.

The analysis will be focused on the FAS population.

4.2.9.5 Sensitivity Analyses of the Tertiary/Exploratory Endpoint

Not applicable.

4.2.9.6 Supplementary Analyses of the Tertiary/Exploratory Endpoint

Not applicable.

4.2.9.7 Subgroup Analyses

Not applicable.

4.2.10 Tertiary/Exploratory Endpoint – Annualised rate of COPDCompEx Event

4.2.10.1 Definition

The COPDCompEx definition and derivation are detailed in AZ Business Rules.

Events regardless of what type (i.e., acute worsening or exacerbation) must be separated by at least 14 days in order to count as separate events (i.e., there must be at least 14 days during which no criteria for events are fulfilled).

The time during the event and the 14 days after each event will not be considered when defining time at risk for the COPDCompEx event rate. Time at risk (days) will be defined as

[Date of last dose of study intervention – date of the first dose of study intervention] + 2 – recovery time.

Where recovery time is defined as:

$$\sum_{i=1}^{k}[min(i^{th}\ event\ end\ date + 14, date\ of\ last\ dose\ of\ study\ intervention) - i^{th}\ event\ start\ date + 1]$$

4.2.10.2 Derivations

Annualised rate of COPDCompEx events, based on the period from baseline to last dose, will be calculated as:

$$\text{Annualised rate of COPDCompEx events} = \frac{\text{Total number of COPDCompEx events}}{(\text{Date of last dose of IP} - \text{Date of the first dose of IP} - \text{recovery time} + 2)/365.25}$$

For participants who do not experience an on-treatment COPDCompEx event, date of censoring will be the last dose date or last date of eDiary recording whichever is earlier.

For CompEx analyses, only on-treatment events (i.e., events occurring from randomisation up to and including the last dose day) will be considered.

4.2.10.3 Handling of Dropouts

The "while on treatment" strategy, same as defined in section 4.2.1.3.

4.2.10.4 Primary Analysis of Tertiary/Exploratory Endpoint

Number of COPDCompEx events, total follow-up time and annualised exacerbation rate including the two-sided 90% CI will be summarised by study intervention group.

The COPDCompEx event rate based on the period during the intervention from baseline through the last dose will be analysed using negative binomial regression (see Section 3.4.4). Rate ratio from AZD4831 compared to placebo will be displayed.

The analyses will be focused on the FAS population, including only those subjects with post-baseline eDiary data.

4.2.10.5 Sensitivity Analyses of the Tertiary/Exploratory Endpoint

Not applicable

4.2.10.6 Supplementary Analyses of the Tertiary/ Exploratory Endpoint

Not applicable

4.2.10.7 Subgroup Analyses

Not Applicable

4.2.11 Tertiary/Exploratory Endpoint – Annualised rate of moderate or severe COPD exacerbations

4.2.11.1 Definition

Defined in section 4.2.2.1. Events must be separated by at least 7 days in order to count as separate events.

4.2.11.2 Derivations

Annualised rate of moderate or severe COPD exacerbations based on the period during the intervention from baseline through the last dose will be calculated as follows:

$$\text{Annualised rate of moderate or severe COPD exacerbations} = \frac{\text{Total number of moderate or severe COPD exacerbations}}{(\text{Date of last dose of IP} - \text{Date of the first dose of IP} - \text{recovery time} + 2)/365.25}$$

Where recovery time is defined as:

$$\sum_{i=1}^{k}[min(i^{th}\ exacerbation\ end\ date + 7, date\ of\ last\ dose\ of\ study\ intervention) - i^{th}\ exacerbation\ start\ date + 1]$$

For participants who do not experience an on-treatment moderate or severe COPD exacerbation event, date of censoring will be the date of last dose.

4.2.11.3 Handling of Dropouts

The “while on treatment” strategy, same as defined in section 4.2.2.3

4.2.11.4 Primary Analysis of Tertiary/Exploratory Endpoint

Number of moderate or severe AECOPD events, total follow-up time and annualised exacerbation rate including the two-sided 90% CI will be summarised by study intervention group.

Number of participants with at least one moderate or severe AECOPD, total number of days of exacerbations, total number of days of exacerbations per participant and total number of exacerbations per participant-treatment year will be summarised by study intervention group.

Annualised rate of moderate or severe COPD exacerbations based on the period during the intervention from baseline through the last dose will be analysed using negative binomial regression (see Section 3.4.4). Rate ratio from AZD4831 compared to placebo will be displayed.

The analyses will be focused on the FAS population.

4.2.11.5 Sensitivity Analyses of the Tertiary/Exploratory Endpoint

Not applicable

4.2.11.6 Supplementary Analyses of the Tertiary/ Exploratory Endpoint

Not applicable

4.2.11.7 Subgroup Analyses

Not Applicable

4.3 Pharmacodynamic Endpoint(s)

4.3.1.1 Definitions and Derivations

Sputum samples will be collected for pharmacodynamic assessments at SV3(Baseline) and SV5(Week 12).

The target engagement will be defined as:

$$100 \times \frac{MPO\ Activity}{MPO\ Concentration}$$

Change from baseline in target engagement to Weeks 12 will be calculated as specified in Section 3.3.1.2.

4.3.1.2 Presentation

The normalised MPO activity and its change from baseline will be summarised using descriptive statistics.

Change from baseline to Weeks 12 in normalised MPO activity will be analysed using a ANCOVA as described in Section 3.4.2.

LSMean change from baseline and two-sided 90% CI to Weeks 12 in normalised MPO activity will be presented.

Participants who had intercurrent events will be included for analysis using treatment policy strategy.

Treatment policy strategy means if an intercurrent event occurs all subsequent data for that participant up to last dose are included in the evaluation.

4.4 Pharmacokinetics

4.4.1 Definitions and Derivations

Blood samples will be collected for measurement of plasma concentrations of AZD4831 at the following timepoints:

- Day 1 Pre-dose
- Week 12:
  - Pre-dose
  - Post-dose (for approximately 20% of participants)
    0.5h to 1.5h post-dose and 1.5h to 3h post, with a minimum of 1h between the post-dose sampling occasions.

Plasma samples will be used to analyse the PK of AZD4831. Samples collected for analyses of AZD4831 concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Pharmacokinetic data for those participants with additional PK sampling at Week 12 will be used to derive plasma PK parameters.

Cmax	Maximum observed plasma concentration
Tmax	Time to reach peak or maximum observed concentration following drug administration
Ctrough	Observed lowest concentration before the next dose is administered

Additional PK parameters may be determined where appropriate.

The derivation of PK parameters from the plasma concentration for AZD4831 will be performed by AstraZeneca CPK scientist team, in accordance with AZ Global Guidance for Non-Compartmental Pharmacokinetic Evaluations in Clinical Studies.

Pharmacokinetic analysis will, where possible, be carried out using actual times determined from the PK sampling and dosing times recorded in the raw data.

4.4.2 Presentation

The PK concentrations and PK parameters will be listed and presented in tabular and graphical form, as appropriate, according to the version of the AstraZeneca Corporate templates and reporting standards as documented in the TFL shells, that include applicable descriptive statistics, defined handling of individual concentrations BLQ and precision/rounding rules for PK concentration and parameter data.

Plasma AZD4831 concentrations will be summarised using descriptive statistics (including geometric mean, CV%) for all timepoints at each visit by study intervention group on PK set and will be listed for each patient from the SS.

Geometric mean (together with gSD) serum AZD4831 concentration over time will be plotted on both linear and semi-logarithmic scales for Week 12 based on PK set. For the 0.5h to 1.5h sample and 1.5h to 3h sample, the geometric mean will be plotted at the midpoint of the collection window (ie 1h and 2.25h respectively).

Individual and combined individual serum AZD4831 concentration vs actual time plots will be provided for the 20% of participants with post-dose PK sampling at Week 12 on both the linear and semi-logarithmic scale.

4.5 Immunogenicity

Not applicable

4.6 Genetics

Not applicable.

4.7 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, ECG and physical examination.

Tables are provided for the safety set; listings are provided for All participants or the safety set depending on the availability of data.

The safety analysis will not be performed as planned in the CSP using estimand strategy. The analyses of adverse events will include all data reported, which includes all data up to the end of the study period including the treatment and follow-up periods, starting from date of the first dose of IP and ending on the earliest date of withdrawal of consent or date of death or last study visit (SV8). For other safety analysis (ie, labs, vital signs), all data up to the end of the study period including the treatment and follow-up periods starting from baseline or screening data and ending on the earliest date of withdrawal of consent or date of death or last study visit (SV8).

4.7.1 Exposure

4.7.1.1 Definitions and Derivations

Exposure duration is calculated only for participants in the Safety population as the total number of days on study drug and is calculated as:

$$Exposure\ duration\ (days) = Last\ drug\ application\ date - First\ drug\ application\ date + 1 - (treatment\ interruption\ period)$$

The date from end of treatment phase is to be used for last drug application date.

Exposure as measured by amount tablets administered calculated as:

$$Actual\ exposure\ (tablets) = tablets\ dispensed - tablets\ returned$$

Note that if any 'Amount Returned' field in the Drug Accountability CRF page is blank, then this formula will not be calculated.

If any of the first or last dates are missing or partially missing, then imputed dates will not be used, and study drug exposure is set to missing.

Total amounts of doses received will be calculated as number of days where at least one dose amount of >0 is administered. The first dose of the intervention period intended to be the SV3 dose and the intended last dose of the intervention period is SV7 dose.

Total time of exposure (patients-years) is calculated as:

$$Total\ time\ of\ exposure\ (patients - years) = \frac{1}{365.25} \times \sum_{Patient} Exposure\ duration$$

4.7.1.2 Presentation

The duration of exposure and total amount of dose received will be summarised using descriptive statistics for each study intervention group and overall.

Duration of exposure and total dose will be presented by category, with categories being Days 1-28, 29-56, 57-84, 85-112, 113-140 and 141-172.

The total time of exposure will be displayed by intervention and overall.

In addition, a figure of exposure over time will be presented, with one line for each study intervention group, and percentage of participants still exposed on the y-axis and time from

first dose on the x-axis. At a given time t, the curve will show the percentage of participants with exposure time >t.

The total amount of dose will be summarised by intervention group and overall.

These outputs will be based on the SS.

Exposure details, such as duration of exposure, date of each treatment administration and dose per administration, will be listed for the Safety population.

4.7.2 Adverse Events

4.7.2.1 Definitions and Derivations

Adverse events (AEs) will be collected from the time of first dose of study intervention throughout the treatment and the follow-up periods (SV8). 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 (SAEs) will be recorded from the time of signing of the ICF. AEs will be coded with MedDRA version 25.1 or higher and will be classified by SOC and PT. For any additional details on AE reporting please refer to the CSP.

AEs will be defined as treatment emergent adverse events (TEAEs) if they have an onset date on or after first dose date of study intervention until safety follow-up. AEs with a missing start date will be considered as TEAEs.

Any AE
Defined as an AE reported with an onset date within the defined period.

Any SAE
Defined as an AE reported as serious, irrespective of outcome.

SAEs with outcome death
Defined as an AE with reported outcome as ‘Fatal’, there may be more than one AE with outcome death for a patient. The onset date of the AE determines the analysis period, irrespective of date of death.

AEs leading to discontinuation of IP
Defined as an AE with action taken IP reported as drug permanently discontinued. The onset date of the AE determines the analysis period, irrespective of date of discontinuation of IP.

AEs possibly related to IP

Defined as an AE that is reported as "reasonable possibility AE caused by IP". If this evaluation is missing, it will be counted as an AE possibly related to IP.

AEs by maximum intensity

AEs will be classified by the reported maximum intensity, "Mild", "Moderate" and "Severe". If this maximum intensity evaluation is missing, it will be counted as "Severe".

Adverse events of special interest

The following AESIs will be particularly monitored in this study:

Skin reactions, including maculopapular rash:

- Skin reactions/rashes considered maculopapular (described as macules/papules under the morphology/appearance question).
- Skin reactions/rashes not considered maculopapular (not described as macules/papules under the morphology/appearance question).

Infections, including pneumonia will be defined by the SOC "Infections and infestations" or the pathogen specific High level group term (HLGT) "Fungal infectious disorders"

AEs will be assigned to a specific category based on investigator's judgement, using a checkbox on the AE CRF page.

4.7.2.2 Presentation

All AE summary tables and listings will be created by study intervention group for the SS, unless otherwise specified. TEAEs occurring during study intervention and follow-up period will be reported in summary tables including any related to the pre-dose orthostatic test at Visit SV3. All AEs will be listed in key subject information tables and listings.

Overview tables will contain number and percentage of participants and number of episodes in following categories:

Any AEs
Any AEs with outcome = death
Any SAEs (including events with outcome = death)
Any AE related to IP (as assessed by the Investigator)
Any AEs leading to discontinuation of IP
Any AEs leading to dose interruption
Any AEs leading to withdrawal from study
Any AESI
Any pneumonia or other serious infection
Any skin reaction

Any maculopapular rash
Any non-maculopapular rash
Any maculopapular rash leading to IP discontinuation, by maximum of CTCAE grade and overall
Any non-maculopapular rash leading to IP discontinuation, by maximum of CTCAE grade and overall

The number and percentage of participants with AE by SOC and PT will be summarised by study intervention group.

The number and percentage of participants with AEs occurring in >5% of participants in any study intervention group will be summarised by PT and study intervention group.

The number and percentage of participants with AEs by maximum reported intensity by SOC and PT will be summarised by study intervention group.

The number and percentage of participants with possibly-related AEs as assessed by investigator will be summarised by:

- SOC, PT and study intervention group
- SOC, PT, maximum grade of severity and study intervention group.

The number and percentage of participants with AEs with outcome of death by SOC and PT will be summarised by study intervention group. Key patient information for participants who experienced AEs with outcome of death will be produced for each study intervention group using following information:

Patient identifier
Sex
Age (years)
Race
Event term as reported by the investigator
PT
Time from first IP administration (days)
Time from last IP administration (days)
Time from last IP administration to death (days)
Time from first IP administration to death (days)
Reasonable possibility AE caused by IP

The number and percentage of participants with SAEs by SOC and PT will be summarised by study intervention group, the summary will be repeated to present number and percentage

of participants with related SAEs. Key patient information for participants who experienced SAEs will be produced using following information:

Study intervention group
Patient identifier
Sex
Age (years)
Race
Event term as reported by the investigator
PT
Time from first IP administration to onset of AE (days)
Time from last IP administration prior to onset of AE (days)
Time from start of IP administration to becoming serious
Outcome
Action taken with IP
Reasonable AE caused by IP

The number and percentage of participants with AEs leading to discontinuation of investigational product by SOC and PT will be summarised by study intervention group. Key patient information for participants who experienced AEs leading to discontinuation of IP will be produced using following information:

Study intervention group
Patient identifier
Sex
Age
Race
AE as reported by the investigator
PT term
Time from first IP administration to onset of AE (days)
Time from last IP administration prior to onset of AE (days)
Seriousness
Outcome
Reasonable possibility AE caused by IP

A list of PTs for AESIs will be produced.

Number and percentage of participants with AESIs will be summarised by category and PT for each study intervention group. Number and percentage of participants with serious AESIs will be summarised by category and PT for each study intervention group.

Number and percentage of participants with skin reactions will be summarised by category, PT and maximum CTCAE grade for each study intervention group. Number and percentage of participants with serious skin reactions will be summarised by category, PT and maximum CTCAE grade for each study intervention group. Additionally to the all AE listing, all skin reactions will be listed separately.

Number and percentage of participants with AESIs will be summarised by category, PT and maximum intensity for each study intervention group. Number and percentage of participants with serious AESIs will be summarised by category, PT and maximum intensity for each study intervention group.

Key patient information for participants who experienced AESI will be produced using following information:

Study intervention group
Patient identifier
Sex
Age
Race
AE Category
AE as reported by the investigator
PT term
Time from first IP administration to onset of AE (days)
Time from last IP administration prior to onset of AE (days)
Seriousness
Maximum Intensity (mild, moderate, severe)
Outcome
Reasonable possibility AE caused by IP

Key patient information for participants who experienced at least one positive sequence suggesting orthostatic hypotension (more details in Section 4.7.6) will be produced using following information:

Study intervention group
Patient identifier
Sex
Age
Race
AE as reported by the investigator
PT term

Time from first IP administration to onset of AE (days)

Time from last IP administration prior to onset of AE (days)

Seriousness

Maximum Intensity (mild, moderate, severe)

Outcome

Reasonable possibility AE caused by IP

Flag for event occurring within 3 hours after first dose of IP for baseline

BP values from VS

Key patient information for participants who experienced at least two positive sequence suggesting orthostatic hypotension (more details in Section 4.7.6) will be produced using same information as above.

Time to onset to maculopapular rash and grade 3 maculopapular rash will be summarised and time to onset to maculopapular rash will be displayed with box plots.

Narratives will be generated for all deaths, AEs leading to discontinuation of IP, AEs of Special interest and SAEs.

4.7.3 Clinical Laboratory, Blood Sample

4.7.3.1 Definitions and Derivations

Following haematology, clinical chemistry, and coagulation parameters will be assessed:

Abnormalities in selected parameters for haematology and chemistry laboratory measurements are defined as post-baseline measurements meeting the pre-defined criteria for abnormality below and is more extreme than the non-missing baseline value for a patient. Thus, if the baseline value met the criteria for marked abnormality and the post-baseline value is equal to or less extreme than the baseline value, this is not considered as abnormal. Low and high ranges are derived based on reference ranges provided by the central laboratory, if available.

Table 10 Laboratory Blood Safety Variables and criterion for abnormality

Parameter	Selected parameters and their criterion for abnormality
Haematology/haemostasis (whole blood)	
B-Haemoglobin (Hb)	• < 100 g/L • < 80 g/L
Eosinophils	• ≥ 0.7 x 10^9/L • ≥1.5 x10^9/L
Neutrophils	• < 1.5 x 10^9/L • < 1.0 x 10^9/L

Parameter	Selected parameters and their criterion for abnormality
Haematology/haemostasis (whole blood)	
B-Leukocyte count	• < 3.0 x 10^9/L • < 2.0 x 10^9/L
B-Platelet count	• < 100 x10^9/L
Clinical chemistry (serum)	
S/P-Creatinine	• ≥ 1.5x baseline creatinine • ≥ 2x baseline creatine
S/P-Bilirubin, total	• ≥2 × ULN
S/P-Aspartate transaminase (AST)	• ≥3 × – <5 × ULN • ≥5 × – <10 × ULN • ≥10 × ULN
S/P-Alanine transaminase (ALT)	• ≥3 × – <5 × ULN • ≥5 × – <10 × ULN • ≥10 × ULN
S/P-Potassium	• ≥ 5.5 mmol/L • ≥ 6.0 mmol/L • ≥ 6.5 mmol/L
S/P-Sodium	• < 135 mmol/L • >145 mmol/L
Coagulation parameters (screening only)	
Prothrombin time (PT)	
Activated partial thromboplastin time (aPTT)	
International normalised ratio (INR)	
Fibrinogen	

Note for serum chemistry: Tests for AST, ALT, ALP and S-bilirubin must be conducted concurrently and assessed concurrently.
ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; aPTT= Activated partial thromboplastin time; AST = Aspartate aminotransferase; B = Blood; CK = Creatine kinase; FSH = Follicle stimulating hormone; Hb = Haemoglobin; INR = International normalised ratio; PT = Prothrombin time; S/P = Serum/Plasma;

4.7.3.2 Presentations

Laboratory evaluations (continuous haematology and clinical chemistry as per Precision tab in mock shells) will be summarised using descriptive statistics at each visit and change from baseline summarised for each post-baseline visit, if available. Haematology and clinical chemistry abnormalities by predefined criteria will also be summarised, and a listing on key patient information supporting the summary will be provided. Coagulation results will be summarized for screening only.

In addition to the summaries above also the maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's law criteria will be presented using the following categories:

Table 11 Category for Liver Function parameters

Liver Function Parameters	Category
ALT	• ≥3 × – <5 × ULN • ≥5 × – <10 × ULN • ≥10 × ULN
AST	• ≥3 × – <5 × ULN • ≥5 × – <10 × ULN • ≥10 × ULN
Total bilirubin	• ≥2 × ULN
Potential Hy's law	• (AST ≥ 3 × ULN or ALT ≥ 3 × ULN) and (Total Bilirubin ≥ 2×ULN)[a]

ULN: upper limit of normal range.
[a]: It includes all participants who have ALT or AST≥3xULN and total bilirubin ≥2xULN, and in which the elevation in transaminases precede or coincide with (that is, on the same day as) the elevation in total bilirubin.

ALT or AST versus total bilirubin, expressed as multiples of ULN as well as liver biochemistry test results over time – participants with elevated ALT or AST, and elevated total bilirubin will be presented in figures. Liver biochemistry results over time will be presented in figures for participants with elevated AST or ALT, and elevated total bilirubin. A separate listing of key information for participants with potential Hy's law will be produced.

A listing of individual laboratory measurements, including reference range indicator will be presented.

The analysis will be focused on the SS.

4.7.4 Clinical Laboratory, Urinalysis

4.7.4.1 Definitions and Derivations

Following urinalysis parameters will be assessed via dipsticks:

Table 12 Laboratory Urinalysis Safety Variables

Urinalysis (dipstick)
U - Leukocytes
U - Nitrite
U- Urobilinogen
U- Protein
U- Blood
U-Ketones
U-Bilirubin
U-Glucose

4.7.4.2 Presentations

Urinalysis results will be summarised in tables by intervention group. A urinalysis listing on key patient information supporting the summary will be provided for patient with urinalysis abnormalities.

The analysis will be focused on the SS.

4.7.5 Other Laboratory Evaluations

4.7.5.1 Definitions and Derivations

Other laboratory tests assessed include FSH (screening only, if needed to confirm postmenopausal status in female participants aged < 50 years only), ANCA, Viral serology at screening only (Hepatitis B, Hepatitis C, HIV-1) and thyroid test (Free T4, T3, Total T4 and TSH).

Table 13 Thyroid criterion for abnormality

Parameter	Selected parameters and their criterion for abnormality
TSH	• >6 mIU/L • ≥10 mIU/L
TSH and free T4	• TSH > 6mIU/L and free T4 < Lower limit normal (LLN) • TSH ≥10mIU/L and free T4 < LLN

4.7.5.2 Presentations

Thyroid functions parameters will be summarised at each visit. Thyroid abnormalities by predefined criteria will also be summarised.

A listing with key patient information will be provided for each other laboratory test for the safety population.

The analysis will be focused on the SS.

4.7.6 Vital Signs

4.7.6.1 Definitions and Derivations

The following vital signs parameters are collected as per SoA (CSP Section 1.3):

Oral or tympanic temperature (collected in ℃ or °F)
Diastolic blood pressure (collected in mmHg)
Systolic blood pressure (collected in mmHg)
Pulse rate (collected in beats/min)
Respiratory rate (collected in breaths/min)

Multiple blood pressure and heart rate measurements will be performed and the average of the measurements will be used for analysis in case the measurements are valid. Valid blood pressure measurements are defined as 2 or more measurements with a maximum difference of 10 mmHg whatever the position (supine/standing/sitting). Valid heart rate measurements are defined as 2 or more measurements with a maximum difference of 10 bpm whatever the position (supine/standing/sitting). All measurements will be considered within a visit in case the measurements are within the range pairwise.

Body mass index at baseline will be calculated from the height (in meters) and weight (in kilograms) as follows: BMI = weight / (height^2).

Additionally, vital signs values will be classified as normal (if value is between lower and upper limit), low (if value is below the lower limit) and high (if value is above the upper limit) according to the normal reference ranges (Table 14):

Table 14 Vital sign reference ranges

Parameter	Standard Unit	Lower limit	Upper limit
Body temperature (oral, tympanic)	°C		≥37.5
DBP	mmHg	<50	≥95
SBP	mmHg	<90	≥160
Heart (pulse) rate	beats/min	<45	>100
Respiratory rate	breath/min	<12	≥25

DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure.
High value (H) is defined as upper reference limit. Low value (L) is defined as below lower reference limit.

Orthostatic BP measurements

Orthostatic BP measurements are obtained using a standard sphygmomanometer after scheduled supine measurements (1 and 3 minutes after the patient 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.

For each visit/timepoint, up to 2 additional orthostatic blood pressure sequences may be performed. For each sequence, the orthostatic hypotension is defined by a decrease (between supine value and values at 1 or 3 minutes after standing) of ≥20 mmHg for SBP or ≥10 mmHg for DBP. The orthostatic hypotension for the visit/timepoint is confirmed if 2 of 2 or 2 of 3 sequences have demonstrated hypotension or if symptoms are reported to have occurred at

any of the sequences. When orthostatic hypotension is confirmed, the investigator reports an "Orthostatic Hypotension" adverse event specifying the date and time.

Details about the orthostatic blood pressure assessment are described in Appendix A.

The following definitions will be applied:

- BP decrease: orthostatic hypotension derived from orthostatic BP data with at least 2 positive sequences (ie. 2 of 2 or 2 of 3).
- BP decrease reported as AE: "Orthostatic Hypotension" AE starting the same day on Day 1 Pre-dose, Day 1 Post-dose or within the same day of the 12 weeks measurement.

The three following timepoints will be considered:

- Day 1 pre-dose
- Day 1 post-dose
- Week 12

For BP decrease, the CRF visit/timepoint variables will be used. For BP decreased reported as AE, these timepoints should be derived from exposure dates and times, and "Orthostatic Hypotension" start dates and times.

4.7.6.2 Presentations

Observed values and change from baseline in vital signs (excluding the orthostatic assessments) will be summarised by study intervention group and visit with descriptive statistics.

The number and percentage of participants with at least one vital sign abnormalities (Low/High values) will be summarised by abnormality criteria and intervention group.

Shift from baseline to maximum on-treatment value in vital signs will be presented by intervention group (using the categories from Table 14).

Key patient information will be produced for vital sign parameters treatment-emergent changes outside predefined criteria (Table 14). All vital signs will be listed.

The number and percentage of participants with orthostatic hypotension (BP decreased and BP decreased reported as an AE) will be summarised by intervention group and visit/timepoint.

Key patient information of participants with at least one positive sequence for orthostatic blood pressure (ie. at least one sequence proving a blood pressure decrease) will be presented. This listing will present the following variables:

- Age, gender, race
- The number of positive sequences at the following timepoints:
    - Day 1 Pre-dose
    - Day 1 Post-dose
    - Week 12

The analysis will be focused on the SS.

4.7.7 Electrocardiogram

4.7.7.1 Definitions and Derivations

Electrocardiograms (ECGs) will be performed at screening visit, SV3 (Day 1) and SV5 (Week 12). ECG variables will be collected, as follows:

Heart rate (beats/min);
RR interval (msec);
QRS interval (msec);
PR interval (msec);
QT interval (msec);
QTcF (msec).
Additionally, QTc interval corrected for heart rate will be calculated directly from the CRF using
Bazett´s correction: $QTcB[msec]=QT[msec]/(RR[sec]^{1/2})$

The outcome of overall evaluation will be recorded as normal/abnormal in CRF, with abnormalities being recorded as clinically significant or not clinically significant and reason for abnormal evaluation being provided.

Additionally, ECG values will be classified as normal (if observed value is within normal reference ranges), low (if observed value is below lower limit of normal range) and high (if observed value is above upper limit of normal range) according to normal reference ranges (Table 15).

Table 15 ECG normal reference ranges

Parameter (standard unit)	Lower limit	Upper limit
Heart rate (beats/min)	<45	>100
RR interval (msec)	<600	>1200
QRS interval (msec)	<80	>120
PR interval (msec)	<120	>200
QT interval (msec)	N/A	>420 male >440 female
QTcB (msec)	N/A	>450
QTcF (msec)	N/A	>450

4.7.7.2 Presentations

Observed values and change from baseline in ECG variables will be summarised by visit using descriptive statistics.

ECG data and ECG abnormalities will be listed.

The analysis will be focused on the SS.

4.7.8 Other Safety Assessments

4.7.8.1 Definitions and Derivations

Physical Examination

A complete physical examination will be performed at Visit SV3 (Day 1) and at Discontinuation visit, including 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 performed at Screening (SV1),Visit SV5 and SV7 will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

The CRF page for physical examination is designed in a way to collect whether the examination was performed, and if so, the date of the examination. Any post-baseline abnormalities in physical examination will be recorded on the AE form.

4.7.8.2 Presentations

As every abnormality in physical examination will recorded on the AE form, the physical examination data will not be reported.

5 INTERIM ANALYSIS

An administrative IA will be conducted after the first 136 COPDCompEx events (70% of the required total 194 events) have occurred. It will allow an early assessment of efficacy for AZD4831 according to the decision framework. No formal statistical test will be conducted. The IA assessment will be used to guide internal (AstraZeneca) decision-making regarding further development of the AZD4831 program. As a result, no alpha will be spent at the IA. A URC will be set up to perform this administrative IA on the primary efficacy endpoint. Details about the execution of the IA will be provided in the URC charter. This will ensure that the study team remains blinded throughout the study conduct and guarantee the integrity and avoid any conscious or unconscious biases.

A subset of TFLs from CSR TFLs will be generated for IA. IA TFLs are indicated in TOC (7 Appendix B).

In addition, the IA results will be used for the evaluation of the safety profile of the drug, by the DRC - see section 9.6 of the CSP.

6 REFERENCES

Bartlett JW, Morris TP, Stensrud MJ, Daniel R. The Hazards of Period Specific and Weighted Hazard Ratios. Statistics in Biopharmaceutical Research June 2020; 12(4):1-2

Frewer, P., Mitchell, P., Watkins, C. and Matcham, J. Decision-making in early clinical drug development. Pharmaceutical Statistics 2016;15(3): 255-263
Objective Cough Endpoint: Standards for Analyzing Cough Data from the VitaloJak Monitoring System, 15th September 2022EXACT user manual v8.0

7 APPENDIX

Appendix A Orthostatic Blood Pressure

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 patient will stand, and BP measurements will be taken at 1 and 3 minutes after the patient 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 16, 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 16 : 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.

Appendix B Table of contents

Table 17: Used versions of reference documents for standard mock shells and SAP

Reference document for standard mock shells and SAP	Version	Date created
AZ Early-Phase Biometrics Content Guidance for RIA SAP		
AZ Corporate CSRHLD Figure Templates v3.2	3.2	30Jun2020
AZ Corporate CSRHLD Listing Templates v1.5	1.5	31Mar2021
AZ Corporate Pandemic CSRHLD Table and Listing Templates v1.3	1.3	31Mar2022
AZ Oncology TA TFL Templates v3.1	3.1	18Dec2020
AZ Respiratory CSRHLD Table and Figure Templates v1.3	1.3	Mar2022
AZ Respiratory Pandemic CSRHLD Table and Listing Templates v1.0	1.0	01Oct2020
AZ_Corporate_Table_Templates_20220408	20220408	08Apr2022
AZ_Respiratory_Immunology_Table_Templates_20220405	20220405	05Apr2022
AZ_Standard_Output_general_principles_20220930_v1	v1	30Sep2022
AZ Corporate CSR/HLD Table Templates	2.0	May2020

TFL number	Title	Standard mock shell reference	Additional Information	IA
14.1 - STUDY POPULATION				
Table 14.1.1	Disposition	AZ_Corporate_Table_Templates_20220408 AZTSP01	Include: • subjects enrolled, • subjects not randomised (incl. reasons), • subjects randomised, o subjects randomised, not treated, o subjects started treatment, o subjects completed the treatment, o subjects discontinued treatment (incl. reasons), • subjects included in the cough substudy, • subjects completed the study and • subjects withdrawn from study (incl. reasons) Add a "Total" column.	no
Table 14.1.2	Recruitment per country and site	AZ_Corporate_Table_Templates_20220408 AZTSP02	A column is added for each analysis set	no
Table 14.1.3	Stratification at randomisation (Randomised set)	AZ_Corporate_Table_Templates_20220408 AZTSP03	To be revised with the stratification factor of the study. Add a "Total" column.	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.1.4	Disposition due to global/country situation (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP04	To be revised with study-specific reasons	no
Table 14.1.5	Global/country situation study disruptions (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP05	To be revised with study design	no
Table 14.1.6	Important protocol deviations (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP06	The categories are revised according to Protocol Deviations Plan	no
Table 14.1.7	Analysis sets	AZ_Corporate_Table_Templates_20220408 AZTSP07	For each analysis set, include reasons for exclusion.	no
Table 14.1.8	Demographics (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP08	Include age, gender, race and ethnicity	Yes
Table 14.1.9	Baseline characteristics (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP09	Include: - height, weight and BMI	Yes
Table 14.1.10	Lung function data at screening (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRISP03	Include:- FEV1, FVC, FEV1/FVC and FEV1% predicted	no
Table 14.1.11	Lung function data at baseline (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRISP03	Include:- Lung functions PEF, FEV1, FVC, FEV1/FVC FEF25-75%, FEV1 and FVC % predicted,and forced inspiratory vital capacity	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.1.12	COPD characteristics at randomisation (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRISP04	Include : - Time since COPD diagnosis - Time to first appearance of COPD symptoms - GOLD Classification - Occurrence of previous admission to ICU for COPD in past 24 months - Number of moderate and severe exacerbation within 24 months prior enrolment - Frequent productive cough - Use of disease-related medications (ICS + LABA + LAMA or ICS + LABA or LABA + LAMA)	no
Table 14.1.13	Medical history by system organ class and preferred term (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP13		no
Table 14.1.14	Prior medication by ATC classification and generic drug name (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP14		no
Table 14.1.15	Prior disease-related medications (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRISP05	Revise column with the disease-related medication. Add a "Total" column.	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.1.16	Concomitant medication by ATC classification and generic drug name (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP15		no
Table 14.1.17	Intercurrent event of restricted medication use (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRISP07		no
Table 14.1.18	Study treatment compliance (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTSP17	Revise footnotes	no
Table 14.1.19	Inhaled tobacco usage characteristics at baseline (Full analysis set)	AZ Corporate CSRHLD Table Templates v3.4 ASP2		no
14.2 - EFFICACY				
14.2.1 - Primary efficacy				
Table 14.2.1.1	Summary for time to first COPDCompEx event: while on treatment (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF06	The following results will be displayed at Weeks 4, 12, 18 and 24: - The number of patients at risk - the number of censored patients - the number of events - Kaplan-Meier estimates and CIAdd the log-rank test.	Yes

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.2.1.2	Summary for time to first COPDCompEx event: treatment policy - Supportive analysis (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF06	The following results will be displayed at Weeks 4, 12, 18 and 24: - The number of patients at risk - the number of censored patients - the number of events - Kaplan-Meier estimates and CI Add the log-rank test.	no
Table 14.2.1.3	Hazard ratio for time to first COPDCompEx event: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value	Yes
Table 14.2.1.4	Hazard ratio for time to first COPDCompEx event: treatment policy - Supportive analysis (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value	no
Table 14.2.1.5	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Frequent Productive Cough: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.2.1.6	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Gender: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.7	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Age: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-valueTo be repeated for each category	no
Table 14.2.1.8	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Race: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.9	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by BMI: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.2.1.10	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Geographic Region: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.11	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Baseline FEV1 as percent of predicted: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.12	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Maintenance medications (ICS): while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.13	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Maintenance medications (LABA/LAMA/ICS): while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-valueTo be repeated for each category	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.2.1.14	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Number of COPD exacerbations in last 24 months: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.15	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Type of site of recruitment: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.16	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by Smoking status: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value To be repeated for each category	no
Table 14.2.1.17	Subgroup Analysis: Hazard ratio for time to first COPDCompEx event by MPO concentration at baseline: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10		no
Figure 14.2.1.1	Time to first COPDCompEx event (days), Kaplan-Meier	AZ Corporate CSRHLD Figure Templates v3.2 E1		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
	plot: while on treatment (Full analysis set)			
Figure 14.2.1.2	Time to first COPDCompEx event (days), Kaplan-Meier plot: treatment policy – Supportive analysis (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E1		no
Figure 14.2.1.3	Time to first COPDCompEx event (days), diagnostic plot (log-log): while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E1		no
Figure 14.2.1.4	Time to first COPDCompEx event (days), diagnostic plot (log-log): treatment policy – Supportive analysis (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E1		no
14.2.2 - Secondary efficacy				
Table 14.2.2.1	Summary for time to first COPD exacerbation event: while on treatment (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF06	The following results will be displayed at Weeks 4, 12, 18 and 24: - The number of patients at risk - the number of censored patients - the number of events - Kaplan-Meier estimates and CI Add the log-rank test.	Yes

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.2.2.2	Hazard ratio for time to first COPD exacerbation event: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF10	Remove the following columns: - Median time to event - Time to percentile - P-value	Yes
Table 14.2.2.3	Summary by visit for post-BD FEV1: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06		no
Table 14.2.2.4	Mean change from baseline in post-BD FEV1 through Week 24: while on treatment (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF01	Remove the following <<Variables>> columns	no
Table 14.2.2.5	Summary by visit for respiratory symptoms: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06	Include in "Page by values" the following parameters: EXACT - total EXACT - breathlessness EXACT - cough & sputum EXACT - chest symptoms BCSS - total BCSS - breathlessness BCSS - sputum BCSS - cough Cough VAS	no
Table 14.2.2.6	Mean change from baseline in respiratory symptoms through Week 24: while on treatment (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF01		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.2.2.7	Summary by visit for total CAT measured in clinic: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06		no
Table 14.2.2.8	Mean change from baseline in total CAT measured in clinic at Week 12 and Week 24: while on treatment (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF01	Remove the following <<Variables>> columns	no
Table 14.2.2.9	Proportion of participants with change from baseline of -2 or less total CAT measured in clinic at week 12: while on treatment (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTBL1b		no
Table 14.2.2.10	Summary by visit for post-BD FEV1: treatment policy - Supportive analysis (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06		no
Table 14.2.2.11	Mean change from baseline in post-BD FEV1 through Week 24: treatment policy - Supportive analysis (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF01	Remove the following <<Variables>> columns	no
Figure 14.2.2.1	Time to first moderate or severe COPD exacerbation (days), Kaplan- Meier plot: while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E1		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Figure 14.2.2.2	Time to first COPD exacerbation event (days), diagnostic plot (log-log): while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E1		no
Figure 14.2.2.3	Change from Baseline in post-BD FEV1 measured in the clinic through Week 12, MMRM - forest plot by subgroup: while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E5	Use the subgroups defined in the SAP.	no
Figure 14.2.2.4	Change from Baseline in EXACT (total and domain scores) through Week 24, LSMeans: while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E6		no
Figure 14.2.2.5	Change from Baseline in BCSS (total and domain scores) through Week 24, LSMeans: while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E6		no
Figure 14.2.2.6	Change from Baseline in cough VAS through Week 24, LSMeans: while on treatment (Full analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 E6		no
Figure 14.2.2.7	Change from Baseline in total CAT measured in clinic through Week 12, LSMeans: while on	AZ Corporate CSRHLD Figure Templates v3.2 E6		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
	treatment (Full analysis set)			
14.2.3 - Secondary efficacy, PK				
Table 14.2.3.1	Plasma concentrations (nmol/L) of AZD4831 over time (PK analysis set)	AZ_Corporate_Table_Templates_20220408 AZTPK02		Yes
Table 14.2.3.2	Pharmacokinetic parameters of AZD4831 (PK analysis set)	AZ_Corporate_Table_Templates_20220408 AZTPK03	Keep only one column for IP. Include only the parameters provided by PK team.	No
Figure 14.2.3.1	Geometric mean (gSD) plasma concentration (nmol/L) of AZD4831 versus time (Linear scale) (PK analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 PK2(i)		no
Figure 14.2.3.2	Geometric mean (gSD) plasma concentration (nmol/L) of AZD4831 versus time (Semi-logarithmic scale) (PK analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 PK2(i)		no
Figure 14.2.3.3	Combined individual plasma concentrations (nmol/L) of AZD4831 versus time (Linear scale) (PK analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 PK3	Individual --> Combined (in order to have several patient on a same plot)Added to cover the semi-logarithmic scale	no
Figure 14.2.3.4	Combined individual plasma concentrations (nmol/L) of AZD4831 versus time (Semi-	AZ Corporate CSRHLD Figure Templates v3.2 PK3	Individual --> Combined (in order to have several patient on a same plot)	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
	logarithmic scale) (PK analysis set)		Added to cover the semi-logarithmic scale	
Figure 14.2.3.5	Individual plasma concentrations (nmol/L) of AZD4831 versus time (Linear scale) (PK analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 PK1		no
Figure 14.2.3.6	Individual plasma concentrations (nmol/L) of AZD4831 versus time (Semi-logarithmic scale) (PK analysis set)	AZ Corporate CSRHLD Figure Templates v3.2 PK1		no
14.2.4 - Tertiary/exploratory efficacy				
Table 14.2.4.1	Summary by visit for average cough frequency: treatment policy (Cough subset)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06	Include in "Page by values" the following parameters: - waking - sleeping - 24h	no
Table 14.2.4.2	Mean change from start of study treatment in average cough frequency after Week 12: treatment policy (Cough subset)	AZ_Corporate_Table_Templates_20220408 AZTEF01	Include in "Page by values" the following parameters: - waking - sleeping - 24h	no
Table 14.2.4.3	Summary by visit for spirometry: treatment policy (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06		no
Table 14.2.4.4	Mean change from baseline in spirometry through Week 24:	AZ_Corporate_Table_Templates_20220408 AZTEF01	Remove the following <<Variables>> columns	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
	treatment policy (Full analysis set)			
Table 14.2.4.5	Summary of sputum MPO activity normalised to sputum MPO concentration: treatment policy (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF06	Only one variable to be analyzed.	no
Table 14.2.4.6	Mean change from baseline in sputum MPO activity normalised to sputum MPO concentration to Week 12: treatment policy (Full analysis set)	AZ_Corporate_Table_Templates_20220408 AZTEF01	Only one variable to be analyzed.	no
Table 14.2.4.7	COPDCompEx recurrent event rates over the period from baseline , negative binomial regression: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF03		Yes
Table 14.2.4.8	COPD exacerbation recurrent event rates over the period from baseline , negative binomial regression: while on treatment (Full analysis set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIEF03		Yes
Figure 14.2.4.1	Box-plot of waking cough frequency by study intervention group and timepoint (Cough subset)	AZ Corporate CSRHLD Figure Templates v3.2 PK5	4 boxplots in total: - 2 arms - 2 timepoints (Baseline + Week 12)	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Figure 14.2.4.2	Box-plot of sleeping cough frequency by study intervention group and timepoint (Cough subset)	AZ Corporate CSRHLD Figure Templates v3.2 PK5	4 boxplots in total: - 2 arms - 2 timepoints (Baseline + Week 12)	no
Figure 14.2.4.3	Box-plot of 24h cough frequency by study intervention group and timepoint (Cough subset)	AZ Corporate CSRHLD Figure Templates v3.2 PK5	4 boxplots in total: - 2 arms - 2 timepoints (Baseline + Week 12)	no
14.3 - SAFETY				
14.3.1 - Drug exposure				
Table 14.3.1.1	Duration of exposure (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTEX01	To be included: - Duration in days - Cumulative categories by every 28th day, from Day 1 to Day 168 - Total time of exposure	Yes
Table 14.3.1.2	Exposure as measured by amount administered (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTEX02	Include the Total amount of doses received.	no
Figure 14.3.1.1	Exposure over time (Safety Set)	AZ Corporate CSRHLD Figure Templates v3.2 S1		no
14.3.2 - Adverse events				

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.2.1	Overall summary of adverse events (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE01	Include: - Any AEs - Any AEs with outcome = death - Any SAEs (including events with outcome = death) - Any AE related to IP (as assessed by the Investigator) - Any AEs leading to discontinuation of IP - Any AEs leading to dose interruption - Any AEs leading to withdrawal from study - Any AESI - Any pneumonia or other serious infection - Any skin reaction - Any maculopapular rash - Any non-maculopapular rash - Any maculopapular rash leading to IP discontinuation, by maximum of CTCAE grade and overall - Any non-maculopapular rash leading to IP discontinuation, by maximum of CTCAE grade and overall	Yes

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.2.2	Adverse events by system organ class and preferred term (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE02	Remove: - "n per 100 subject years" column - AE row category Footnote to be updated.	Yes
Table 14.3.2.3	Adverse events sorted by decreasing frequency on preferred term level in AZ total treatment arm (frequency of > 5%) (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTAE03	Preferred terms are selected if frequency >5% in at least one treatment arm.	no
Table 14.3.2.4	Adverse events by maximum reported intensity on system organ class and preferred term (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTAE04	Remove: - "n per 100 subject years" columnUse category column for maximum reported intensityFootnote to be updated.	no
Table 14.3.2.5	Possibly related adverse events by system organ class and preferred term (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTAE07	Remove: - "n per 100 subject years" column - AE row category Footnote to be updated.	no
Table 14.3.2.6	Possibly related adverse events by maximum intensity and system organ class and preferred term (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE04	Remove: - "n per 100 subject years" column Use category column for maximum reported intensity Footnote to be updated.	no
14.3.3 - Deaths				

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.3.1	Serious adverse events with outcome death by system organ class and preferred term (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE02	Remove: - "n per 100 subject years" column - AE row category Footnote to be updated.	Yes
Table 14.3.3.2	Serious adverse events with outcome death – Key subject information (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTAE13		Yes
14.3.4 - Serious adverse events				
Table 14.3.4.1	Serious adverse events by system organ class and preferred term (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE02	Remove: - "n per 100 subject years" column - AE row category Footnote to be updated.	Yes
Table 14.3.4.2	Possibly related serious adverse events by system organ class and preferred term (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE02	Remove: - "n per 100 subject years" column - AE row category Footnote to be updated.	no
Table 14.3.4.3	Serious adverse events – Key subject information (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTAE17		Yes
14.3.5 - Discontinuation of investigational product due to adverse events				
Table 14.3.5.1	Adverse events leading to discontinuation of investigational product by system organ class and preferred term (Safety set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE02	Remove: - "n per 100 subject years" column - AE row categoryFootnote to be updated.	Yes

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.5.2	Adverse events leading to discontinuation of investigational product - Key subject information (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTAE19		Yes
14.3.6 - Other significant adverse events				
Table 14.3.6.1	Adverse events of special interest - mapping	AZ_Corporate_Table_Templates_20220408 AZTAE20		no
Table 14.3.6.2	Adverse events of special interest by category and preferred term (Safety Set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE03		Yes
Table 14.3.6.3	Adverse events of special interest – Key subject information (Safety Set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE06		Yes
Table 14.3.6.4	Serious adverse events of special interest by category and preferred term (Safety Set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE03		no
Table 14.3.6.5	Adverse events of special interest by maximum intensity grade on category class and preferred term (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTAE04		no
Table 14.3.6.6	Serious adverse events of special interest by maximum reported intensity on category class and preferred term (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTAE04		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.6.7	Skin reactions by CTCAE grade on category class and preferred term (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTAE04		Yes
Table 14.3.6.8	Serious skin reactions by CTCAE grade on category class and preferred term (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTAE04		no
Table 14.3.6.9	Time to onset to First Maculopapular rash (Safety Set)	AZ Oncology TA TFL Templates v3.1 TAE300		no
Table 14.3.6.10	Adverse events – Key subject information - Patients with at least one test sequence suggestive of Orthostatic hypotension (Safety Set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE06		no
Table 14.3.6.11	Adverse events – Key subject information - Patients with at least two test sequence suggestive of Orthostatic hypotension (Safety Set)	AZ_Respiratory_Immunology_Table_Templates_20220405 AZTRIAE06		no
Figure 14.3.6.1	Box-plot of Time to onset to First Maculopapular rash (Safety Set)	AZ Corporate CSRHLD Figure Templates v3.2 PK5		no
14.3.7 - Laboratory				

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.7.1	Haematology results over time (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB01	Include: - Q1 and Q3 - Change from baseline Use <<Page by values>> for each parameter	no
Table 14.3.7.2	Haematology abnormalities by predefined criteria (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB03	See Table 10 for parameters to be included and abnormality criteria	Yes
Table 14.3.7.3	Haematology abnormalities by predefined criteria - Key subject information (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB04		no
Table 14.3.7.4	Chemistry results over time (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB06	Include: - Q1 and Q3 - Change from baselineUse <<Page by values>> for each parameter	no
Table 14.3.7.5	Chemistry abnormalities by predefined criteria (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB08	See Table 10 for parameters to be included and abnormality criteria	Yes
Table 14.3.7.6	Chemistry abnormalities by predefined criteria - Key subject information (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB09		no
Table 14.3.7.7	Coagulation results at Screening (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB06	Include: - Q1 and Q3 Use <<Page by values>> for each parameter	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.7.8	Maximum on-treatment ALT and AST versus maximum on-treatment total bilirubin (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB11		no
Table 14.3.7.9	Potential Hy's law – Key subject information (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB12		no
Table 14.3.7.10	Thyroid function results over time (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB06	Include: - Q1 and Q3 - Change from baseline Use <<Page by values>> for each parameter	no
Table 14.3.7.11	Thyroid abnormalities by predefined criteria (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB08	See Table 11 for parameters to be included and abnormality criteria	Yes
Table 14.3.7.12	Thyroid abnormalities by predefined criteria - Key subject information (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTLB09		no
Figure 14.3.7.1	ALT versus total bilirubin, expressed as multiples of ULN (Safety Set)	AZ Corporate CSRHLD Figure Templates v3.2 S9		no
Figure 14.3.7.2	AST versus total bilirubin, expressed as multiples of ULN (Safety Set)	AZ Corporate CSRHLD Figure Templates v3.2 S9		no
Figure 14.3.7.3	Liver biochemistry test results over time - subjects with elevated ALT or AST, and	AZ Corporate CSRHLD Figure Templates v3.2 S10		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
	elevated total bilirubin (Safety Set)			
14.3.8 - Vital signs				
Table 14.3.8.1	Vital sign results over time (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTVS01	Include: - Q1 and Q3 - Change from baseline Use <<Page by values>> for each parameter	no
Table 14.3.8.2	Vital sign abnormalities by predefined criteria (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTVS03	Abnormality criteria are defined by Low and High, based on Lower and Higher limits values for each parameter.	Yes
Table 14.3.8.3	Vital sign shift from baseline to maximum on-treatment value (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTVS05	The categories are:Low < Normal < High	no
Table 14.3.8.4	Vital sign abnormalities by predefined criteria - Key subject information (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTVS04		no
Table 14.3.8.5	Summary of orthostatic hypotension related measurements (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTVS03	For parameter/Criteria are : - BP decrease - BP decrease reported as an AE Add a column for the timepoints : - Post first dose - Only post first dose - Week 12	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Table 14.3.8.6	Orthostatic blood pressure decrease - Key subject information (Safety set)	AZ_Corporate_Table_Templates_20220408 AZTVS04	This listing will include : - Age, gender, race - The number of positive sequences at the following timepoints: - Day 1 pre-dose - Day 1 post-dose - Week 12	no
14.3.9 - ECG				
Table 14.3.9.1	Electrocardiogram results over time (Safety Set)	AZ_Corporate_Table_Templates_20220408 AZTEC01	Include: - Q1 and Q3 - Change from baseline Use <<Page by values>> for each parameter	Yes
APPENDIX				
Appendix 16.1.1	Subjects receiving the various batches of investigational products	AZ Corporate CSRHLD Listing Templates v1.5 APL22		no
Appendix 16.1.2	Randomisation scheme and codes (Randomised set)	AZ Corporate CSRHLD Listing Templates v1.5 APL23		no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Appendix 16.2.1.1	Discontinued subjects (Randomised set)	AZ Corporate CSRHLD Listing Templates v1.5 APL01	Provide definition of exposure in the footnote Actual exposure is optional If the race Other was collected in the study, a separate column may be added after the Age/Sex/Race column. Sort this listing by: Short subject identifier, Description of planned arm, Start date/Time of disposition event. Standardised disposition terms should include: • Informed consent obtained • Randomisation • Study discontinued due to <<insert reason for discontinuation from EOS form in lower case, e.g. adverse event >>	no
Appendix 16.2.1.2	Subjects completing the study (Randomised set)	AZ Corporate CSRHLD Listing Templates v1.5 APL02	Optional.Standardised disposition terms should include:• Informed consent obtained• Randomisation• Study completed	no
Appendix 16.2.1.3	Subjects affected by the COVID-19 pandemic (Screened set)	AZ Corporate Pandemic CSRHLD Table and Listing Templates v1.3 APL-COVID1	This listing is to satisfy the FDA Guidance which requires A listing of all participants affected by the COVID-19 related study	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
			disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.	
Appendix 16.2.1.4	Adverse events in patients reporting COVID-19 AEs (Safety set)	AZ Respiratory Pandemic CSRHLD Table and Listing Templates v1.0 APL_COVID1	This listing is to satisfy the FDA Guidance which requires A listing of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.	no
Appendix 16.2.1.5	Subjects affected by the global/country situation	AZ Corporate CSRHLD Listing Templates v1.5 APL24		no
Appendix 16.2.1.6	Subjects affected by the global/country situation - details	AZ Corporate CSRHLD Listing Templates v1.5 APL25		no
Appendix 16.2.2	Subjects with important protocol deviations (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL03	Sort this listing by: Short subject identifier, Description of planned arm, Date/Time of collection.	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Appendix 16.2.3	Subjects excluded from any analysis set (Screened set)	AZ Corporate CSRHLD Listing Templates v1.5 APL04	Sort this listing by: Short subject identifier, Description of planned arm. Add column for Description of Actual arm.	no
Appendix 16.2.4	Demographic and baseline characteristics (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL06	Sort this listing by: Short subject identifier, Description of planned arm. Add column for Description of Actual arm.	no
Appendix 16.2.4.2.1	Lung function data at screening (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL07		no
Appendix 16.2.4.2.2	Lung function data at baseline (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL07		no
Appendix 16.2.4.2.3	Inhaled tobacco usage (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL07		no
Appendix 16.2.4.3	Concomitant medication on entry and during the study (Randomised set)	AZ Corporate CSRHLD Listing Templates v1.5 APL08		no
Appendix 16.2.5	Administration of investigational product (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL09	Sort this listing by: Short subject identifier, Description of planned arm, Date first dose (and/or Administration time, if relevant). Columns in the example listing presenting data that are not collected or derived can be	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
			excluded. The listing should be adjusted according to the administration data collected and the type of study/treatment.	
Appendix 16.2.6.1.1	Individual efficacy response data - COPDCompEx events (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL10	Sort this listing by: Short subject identifier, Description of planned arm. Add column for Description of Actual arm.	no
Appendix 16.2.6.1.2	Individual efficacy response data - COPD exacerbations (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL10	Sort this listing by: Short subject identifier, Description of planned arm. Add column for Description of Actual arm.	no
Appendix 16.2.6.1.3	Efficacy assessment(s) - Spirometry measured face to face (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL11	Drop “Site of assessment” and “Method of assessment” columns. “Parameter” are: - absolute and % predicted (as applicable) PEF - FEV1 - FVC - FEV1/FVC - forced mid-expiratory flow (FEF25-75%) - FEV1 and FVC % predicted,	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
			- forced inspiratory vital capacity	
Appendix 16.2.6.1.4	Efficacy assessment(s) - Respiratory symptoms (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL11	Drop “Site of assessment” and “Method of assessment” columns.“Parameter” are: EXACT - totalEXACT - breathlessnessEXACT - cough & sputumEXACT - chest symptomsBCSS - totalBCSS - breathlessnessBCSS - sputumBCSS - coughCough VAS	no
Appendix 16.2.6.1.5	Efficacy assessment(s) - CAT (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL11		no
Appendix 16.2.6.1.6	Efficacy assessment(s) - Cough measures (Cough subset)	AZ Corporate CSRHLD Listing Templates v1.5 APL11	Include 24h, waking and sleeping cough frequencies	no
Appendix 16.2.6.1.7	Efficacy assessment(s) - Sputum MPO activity normalised to sputum MPO concentration (Full analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL11	Sort this listing by: Short subject identifier, date/time and test.	no

TFL number	Title	Standard mock shell reference	Additional Information	IA
Appendix 16.2.6.2.1	Individual plasma AZD4831 concentrations (<UNIT>) (PK analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL30	Sort this listing by: Short subject identifier and date/time.	Yes
Appendix 16.2.6.2.2	Individual AZD4831 pharmacokinetic parameters for each study intervention group (PK analysis set)	AZ Corporate CSRHLD Listing Templates v1.5 APL28	Sort this listing by: Short subject identifier, date/time and parameter.	no
Appendix 16.2.7.1	Adverse events (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL14	Include all AEs Sort this listing by: Short subject identifier, AE start date.	Yes
Appendix 16.2.7.2	Adverse events, skin reaction/rash (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL14	Sort this listing by: Short subject identifier, AE start date.	Yes
Appendix 16.2.8	Individual laboratory measurement (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL16	Sort this listing by: Short subject identifier, Lab test, Analysis visit, planned time point name.	Yes
Appendix 16.2.9	Individual vital signs data (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL18	Sort this listing by: Short subject identifier, test, Analysis visit, planned time point name.	Yes
Appendix 16.2.10.1	Electrocardiogram data (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL19	Sort this listing by: Short subject identifier, test, Analysis visit, planned time point name.	Yes
Appendix 16.2.10.2	Abnormalities in electrocardiogram (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL20		Yes

TFL number	Title	Standard mock shell reference	Additional Information	IA
Appendix 16.2.11	Weight, Height and BMI (Safety set)	AZ Corporate CSRHLD Listing Templates v1.5 APL21		Yes