Statistical Analysis Plan	
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A Phase II, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of MEDI3506 in Participants with Moderate to Severe Chronic Obstructive Pulmonary Disease and Chronic Bronchitis (FRONTIER 4)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACM	Ambulatory Cough Monitoring
ADA	Anti-drug Antibody
ADAM	Analysis Data Model
AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AER	Annual Event Rate
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AO	Airwave Oscillometry
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
CCI [redacted]	
AX	Area of Reactance
B	Blood
BCSS	Breathlessness, Cough and Sputum Scale
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood Pressure
CCI [redacted]	
CCI [redacted]	
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COPDCompEx	Composite endpoint for COPD exacerbations
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CCI [redacted]	
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CV%	Coefficient of variation

Abbreviation or special term	Explanation
d	Day
DBP	Diastolic Blood Pressure
$DPM_{gastrap}$	Disease Probability Measure Gas Trapping
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
E/D	Early Study Intervention Discontinuation Visit
eDiary	Electronic Diary
ePRO	Electronic Patient Reported Outcome
E-RS:COPD	Evaluating Respiratory Symptoms of COPD
ERS	European Respiratory Society
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FEV_1	Forced Expiratory Volume in 1 Second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
gCV%	Geometric coefficient of variation
GGT	Gamma-glutamyl Transferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HIV	Human Immunodeficiency Virus
HL	Hy's Law
CCI [redacted]	
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroids
Ig	Immunoglobulin
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
IMP	Investigational Medicinal Product
IP	Investigational Product
IPD	Important Protocol Deviation
ISR	Injection Site Reaction

Abbreviation or special term	Explanation
ITT	Intention-to-Treat
IV	Intravenous
LABA	Long Acting Beta 2 Agonist
LAMA	Long Acting Muscarinic Receptor Antagonist
LLOQ	Lower Limit of Quantification
LSMean	Least square mean
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Repeated measures mixed effects analysis of covariance model
CCI [redacted]	
MRD	Minimum required dilution
NR	Not Reportable
NT-proBNP	N-terminal pro-brain natriuretic peptide
OCS	Oral Corticosteroids
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDP	Protocol Deviation Plan
PEF	Peak Expiratory Flow
CCI [redacted]	
PI	Principal Investigator
PK	Pharmacokinetics
PNV	Predicted Normal Values
Q4W	Every 4 Weeks
R	Randomization
R5/20	Resistance at 5/20 Hz
RBC	Red Blood Cell
S	Serum
SABA	Short-Acting Beta Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard deviation
SGRQ	St George's Respiratory Questionnaire

Abbreviation or special term	Explanation
SIDES	Subgroup Identification Based on Differential Effect Search
SMQ	Standardised MedDRA Query
SoA	Schedule of Activities
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
SV	Study Visit
TB	Tuberculosis
TC	Telephone Contact
TFL	Tables, Figures and Listings
U	Urine
ULN	Upper Limit of Normal
V	Visit
VAS	Visual Analogue Scale

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	Rationale
Other: objectives	11May2023	Section 1.1: Objectives have been updated	Updates according to CSP Amendment 5.
Other: exploratory endpoints	11May2023	CCI [redacted]	CCI [redacted]
Other: exploratory endpoints	11May2023	CCI [redacted]	Updates according to CSP Amendment 2.
Other: exploratory endpoints	11May2023	CCI [redacted]	Added as per request from the team.
Statistical analysis method for the primary or secondary endpoints	11May2023	Sections 1.2, 1.3 Update of numbers of participants and sample size justification. Section 3.2.4 Added number of COPD exacerbations within previous 24 months.	Updates according to CSP Amendment 5
Other: analysis sets	11May2023	Section 2.1 Subjects enrolled, subjects randomized description added. PK population description updated.	Clarification of analysis population.
Other: definition of baseline	11May2023	Section 3.1.1 CCI [redacted] BCSS score, E-RS:COPD score, Cough VAS, CCI [redacted] we will now considered the baseline if there are at least 7 completed days instead of 10 days.	In order to maximise the number of patients with baseline CCI [redacted]

Other: definition of baseline	11May2023	Section 3.1.1 CompEx added to the baseline definition list. Details of evening and following morning provided.	CompEx will use the same baseline than other e-diary PRO (average of the last two weeks prior to the first dose with at least 7 completed days).
Other: handling of missing data	11May2023	Section 3.1.4 Missing ADA results at baseline will be considered as negative.	As requested by the team.
Other: handling of missing data	11May2023	Section 3.1.4.1 Updated imputation of partial missing AE dates. Section 3.1.4.2 Updated imputation of partial missing medication dates. Section 3.1.4.3 Updated imputation of partial missing COPD history dates.	Updated to avoid any inconsistent information with ADAM variables; to take into consideration the case where a day is entered and not the month; to distinguish imputation of partial missing start and end dates.
Data presentations	11May2023	Section 3.1.5 Added clarification for screening and re-screening visits. CCI [redacted] Added visit windowing for coagulation, CCI [redacted] CCI [redacted] and cough monitoring. PK will have no analysis visit windows, the CRF visit will be used instead. Updated labelling of weekly periods for CCI [redacted] and eDiary variables. Section 3.1.6 Updated of vital signs timepoint labelling. Sections 3.1.7, 3.8.1 Study phase windows have been updated.	Updated to avoid issues that could occur during analyses.
Statistical analysis method for the primary or secondary endpoints	11May2023	Subgroup analysis: Sections 3.1.9, 4.2.5.1, 4.2.5.3, 4.2.8.2: Subgroup analysis of extent of emphysema for secondary CCI [redacted] endpoints has been added.	Updates according to CSP Amendment 4, Amendment 5 and as per requests from the team.

		Sections 3.1.9 and 3.2.1 updated geographical region subgroup: North America has been merged with Western Europe CCI [redacted] CCI [redacted] Section 3.1.9 and 3.2.1: Age subgroup updated. CCI [redacted] Added clarification regarding modalities of subgroups.	
Other: new countries	11May2023	Section 3.2.1: Australia, New Zealand, Czech Republic added.	Updates due to addition of new countries to the study.
Other: smoking status	11May2023	Sections 3.2.5, 4.2.3.5: added definition and details for the overall smoking status. Sections 3.1.9, 4.2.5.1, 4.2.8.3, 4.2.8.4, 4.2.8.5: added new analysis by smoking status subgroup.	Added as per request from the team.
CCI [redacted]	CCI [redacted]	CCI [redacted]	CCI [redacted]
Other: COPDCompEx	11May2023	Section 3.3.4 Lack of efficacy rules removed. Replace evening/morning pairing instead of morning/evening. On-treatment events definition added. Section 3.3.4.1 Updated date of censoring. Section 4.2.5.1 CompEx criteria by patient will be also listed.	Removed "Lack of efficacy" since it is not one of the reason possible in case of treatment discontinuation. Updated pairing to be consistent with other endpoints in the study. Date of censoring was updated to avoid any issues with patients which stopped providing eDiary information before end of treatment.

Other: SGRQ	11May2023	Sections 3.4.4, 4.2.5.5 analyses by domain score for SGRQ will be also provided.	To get detailled results from each domain score and not only for the total score.
Other: immunogenicity variables	11May2023	Sections 3.6.1 and 3.6.2: Removed nAb response.	Removed as we will not need the nAb for this study.
Data presentations	11May2023	Sections 3.8.2 and 4.2.10.3: Specify parameters for coagulation and add fibrogen in coagulation.	Fibrinogen is listed as coagulation in SAP rather than clinical chemistry parameter in CSP (Change from the CSP).
Data presentations	11May2023	Section 3.8.4 Updated ECG normal reference ranges.	Updated following up discussion with medical team.
Other: exploratory endpoints	11May2023	CCI	CCI
CCI	11May2023	CCI	CCI
Other: exploratory endpoints	11May2023	CCI	CCI
Data presentations	11May2023	Section 4.1 Limitation for the number of decimal places. Specified the rule for the values presented in listings. DCO will applies for primary and end of treatment analyses. Added clarification for incorrectly stratified patients.	Added limitation in case if some of the original values are 3 decimal places or more. Updates made following up discussion with the team.

Statistical analysis method for the primary or secondary endpoints	11May2023	CCI [redacted]	CCI [redacted]
Statistical analysis method for the primary or secondary endpoints	11May2023	Sections 4.1.2 and 4.1.3 Removed percent change from baseline definition	Updated since there is no analysis in the study where the percent change from baseline will be used.
Other: Sensitivity analyses	11May2023	Section 4.2.4.3 A sensitivity analysis will be performed excluding data where the Spirometry Vendor have identified the results to be 'implausible'	Added as per request from the team
Data presentations	11May2023	Section 4.2.1 Clarification for total number of patients presented.	Added as per request from the team and to be consistent with TFLs.
Other: adverse events		Sections 4.2.7, 4.2.10 Added summary of AEs by ADA status.	In order to provide the number of AE by ADA status.
Other: adverse events	11May2023	Section 4.2.10.1, 4.2.10.6 Added all Covid-19 related AE tables and other safety test related to Covid-19.	Additional request from the team.
Data presentations	11May2023	Section 4.2.10.3 Category for Liver Function parameters table have been added.	Added to be used in the TFLs.
Other	11May2023	Section 6 few changes have been added compare to the CSP.	The model will used the log of eosinophils at baseline in the models

			instead of eosinophil strata (Change from the CSP).
Other	11May2023	Appendix A list of outputs have been updated	Following the above update, the list of outputs have been evolved.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

1.1 Study objectives

Table 1 Primary objective and associated endpoint

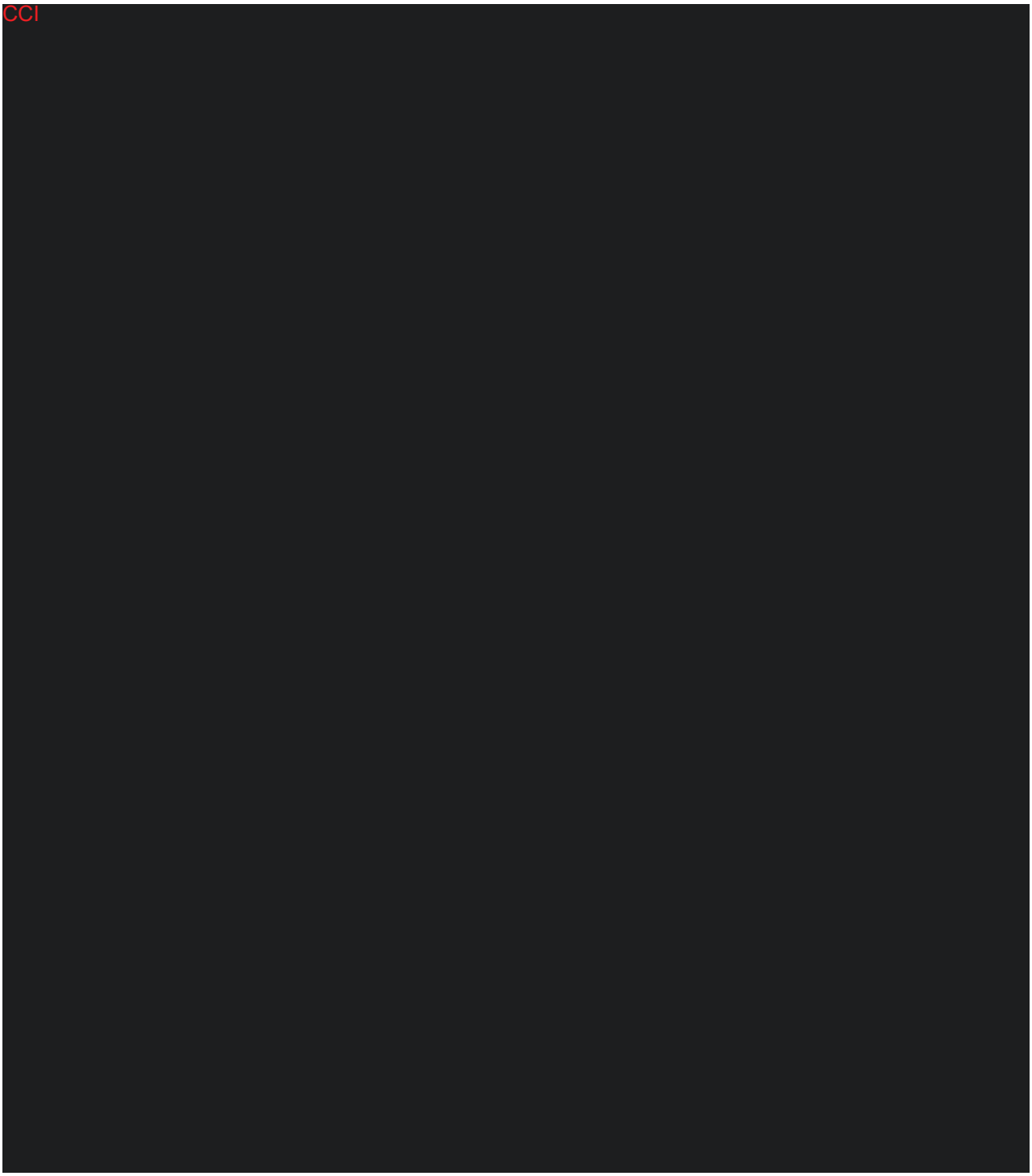
Objective	Endpoint
To assess the effects of MEDI3506 compared with placebo on pulmonary function in participants with COPD and chronic bronchitis.	Change from baseline to Week 12 in pre-BD FEV_1 measured in clinic.

BD = Bronchodilator; COPD = Chronic obstructive pulmonary disease; FEV_1 = Forced expiratory volume 1 second.

Table 2 Secondary objectives and associated endpoints

Objectives	Endpoints
To assess the PK of MEDI3506 in participants with COPD and chronic bronchitis.	Serum MEDI3506 concentration-time profiles during the intervention and follow-up periods.
To assess the immunogenicity of MEDI3506 compared with placebo in participants with COPD and chronic bronchitis.	Anti-drug antibodies during the intervention and follow-up periods.
To assess the effect of MEDI3506 on COPDCompEx event in participants with COPD and chronic bronchitis.	Time to first COPDCompEx event based on the period from baseline to 4 weeks after last dose (Week 28)
To assess the effect of MEDI3506 compared with placebo on respiratory symptoms in participants with COPD and chronic bronchitis.	Change from baseline to Week 12 in: • E-RS:COPD • Mean BCSS score (over the previous 4 weeks) • Cough VAS item
To assess the effect of MEDI3506 compared with placebo on disease impact in participants with COPD and chronic bronchitis.	• Change from baseline to Week 12 in SGRQ total score • Proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 12
To assess the effect of MEDI3506 compared with placebo on airway resistance and reactance in participants with COPD and chronic bronchitis.	Change from baseline to Week 12 in AO parameters: • R5-R20 • R5 • R20 • AX
To evaluate the effect of MEDI3506 compared with placebo on objective cough measures in participants with COPD and chronic bronchitis.	At Week 12, ratio to baseline in: • Daily (ie, 24 hour) cough frequency • Night time cough frequency • Awake time cough frequency
To evaluate the effect of MEDI3506 or placebo on lung function by extent of baseline emphysema on CT scan.	• Change from baseline in pre-BD and post-BD FEV_1 through Week 28 • Change from baseline in pre-BD and post BD FVC through Week 28

AO = Airwave Oscillometry; AX = Area of reactance; BCSS = Breathlessness, cough and sputum scale; COPD = Chronic obstructive pulmonary disease; COPDCompEx = COPD Composite Exacerbations; E-RS:COPD = Evaluating Respiratory Symptoms of COPD; PK = Pharmacokinetic; R5 = Resistance at 5 Hz; R20 = Resistance at 20 Hz; SGRQ = St. George's Respiratory Questionnaire; VAS = Visual analogue scale.



Objectives	Endpoints
CCI	

Objectives	Endpoints
CCI	
CCI	

Table 4 Safety objectives and associated endpoints

Objective	Endpoint
To assess the safety and tolerability of MEDI3506 compared with placebo in participants with COPD and chronic bronchitis.	During the intervention and follow-up periods: • AEs, SAEs, AESIs. • Vital signs. • Clinical chemistry, haematology, and urinalysis. • ECGs. • LVEF as measured by echocardiogram. • NT-proBNP. • For participants testing positive for SARS-CoV-2 (by nucleic acid or serology test),

Objective	Endpoint
	during the intervention and follow-up periods, the number and proportion of patients with COVID-19 AEs/SAEs and the proportion asymptomatic. • Number of participants seropositive for SARS-CoV-2 at end of study who were seronegative at randomization visit.

AE = Adverse event; AESI = Adverse event of special interest; COPD = Chronic obstructive pulmonary disease; COVID-19 = Coronavirus disease 2019; ECG = Electrocardiogram; LVEF = Left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; SAE = Serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1.2 Study design

This is a Phase II, randomized, double-blind, placebo-controlled, proof-of-concept study to assess the efficacy, safety and tolerability of MEDI3506, administered SC Q4W for 7 doses, in participants with moderate or severe COPD receiving standard of care (dual or triple therapy) as maintenance therapy, with a history of ≥ 1 moderate or severe acute exacerbation in the previous 24 months while on stable background treatment, and moderate to severe chronic bronchitis, with active sputum and cough symptoms. The intervention period lasts 28 weeks (7 doses).

Approximately 144 participants will be randomized in a 1:1 ratio to placebo or CCI of MEDI3506 SC Q4W, for 7 doses. The randomization will be stratified by CCI and background medication (includes ICS (Inhaled Corticosteroids) vs does not include ICS).

There are 3 study periods: screening and run-in; intervention period; and follow-up.

The general study design is summarised in Table 5.

Table 5 Study Design

Study Period	Screening / Run-in	Intervention Period					Follow-up
Visit Number	SV1 and SV2	SV3	SV4 to SV7	SV8	SV9 to SV11	SV12	SV13 and SV14
Study Week	-5 to -1	0	0 to 8	12	16 to 24	28	32 to 36
	Enrolment, Screening, Run-in	Randomization and Dose 1	Doses 2 and 3	Primary Endpoint Assessment and Dose 4	Doses 5 to 7	End of Intervention Visit	Follow-up

R = randomization; SV = study visit.

There will be one sub-study in this trial:

CCI [redacted]

1.3 Number of participants

A sample size of 140 participants (70 participants per arm) will provide 80% power to detect a difference in mean change from baseline in FEV_1 at Week 12 of 90 mL (assumed SD of 250 mL) between the 2 randomized groups at a one-sided 10% level of statistical significance. To allow for 2% of participants being ineligible for the primary analysis, approximately 144 participants will be randomized in the study (72 per arm).

CCI [redacted]

CCI [redacted]

2 ANALYSIS SETS

2.1 Definition of analysis sets

The following populations are defined:

Table 6 Populations for analysis

Population/Analysis set	Description
All Subjects/subjects enrolled	Participants who have signed the informed consent form during screening period. Participants who have been randomized will be analysed according to their randomized study intervention group.
All randomized subjects	Participants who are randomized. Participants will be analysed according to their randomized treatment group.
ITT population	Participants who are randomized and receive any study intervention. Participants will be analysed according to their randomized study intervention group.
As-treated Population	Participants who are randomized and receive any study intervention. Participants will be analysed according to the study intervention they actually receive.
PK population	Participants who received at least one dose of MEDI3506 and had at least one detectable serum concentration measurement post first dose of study

Table 6 Populations for analysis

Population/Analysis set	Description
	intervention. A participant is considered as having at least one detectable serum concentration measurement post first dose if has at least one plasma concentration that is not below the LLOQ after the first dose. Participants will be analysed according to the study intervention they actually receive.
CCI	CCI

CCI ITT = Intent to treat; PK = pharmacokinetic(s).

'All Subjects/subjects enrolled' population will be used to summarise all participants disposition. "All randomized subjects" will be used to summarise all randomized patients including the patient randomized but not treated. The ITT population will be used to summarise all demographic and baseline characteristics, concomitant medications, and efficacy measures. CCI The As-treated population will be used to summarise all safety measures (AEs, ADA, laboratory tests, ECG, and vital signs). The PK population will be used to summarise PK measures.

2.2 Violations and deviations

An Important Protocol Deviation, per ICH definition is "a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or wellbeing."

The list of study specific IPDs is provided in the AstraZeneca Protocol Deviations Plan (PDP).

In addition, all protocol deviations and major issues related to COVID-19 will be captured with the prefix "COVID19" for CSR reporting.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General principles

3.1.1 Definition of baseline

In general, the last measurement prior to first injection of IP will serve as the baseline measurement for efficacy and safety endpoints. If Visit 3 (Week 0) measurement is missing, the last non-missing value before Visit 3 (Week 0) will be used as baseline instead. If there is no result collected prior to Visit 3, then baseline value will be set to missing and will not be imputed. In the scenario where there are two assessments on Visit 3 (Week 0) prior to first

dose, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline.

An exception from the general rule will be ECGs - the mean value of each parameter from the repeated pre-dose measurements at Visit 3 (Week 0) will be recorded in eCRF and used as the baseline value.

For CCI [redacted] BCSS score, E-RS:COPD score, Cough VAS, CCI [redacted] baseline would be defined as the average from last 2 weeks (14 days) results prior to first dose of investigational product (Visit 3), ie, 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 for the diary data used in the CompEx analysis will use the same rules. The baseline cough frequency is derived from the cough monitoring performed at Visit 2 (or Rescreening Visit 2 for rescreened participants).

3.1.2 Study day

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.

3.1.3 Absolute and percent change from baseline

Absolute and percent change from baseline will be derived as follows:

Absolute change from baseline outcome variables = (post-randomization value – baseline value).

Percent change from baseline = ((post-randomization value – baseline value) / baseline value) × 100.

For any variable subjected to log transformation, the change from baseline calculated and summarised on the log scale will be back transformed and presented as a ‘baseline scaled ratio’ (BSR). Percentage change will then be calculated as (BSR - 1) x 100.

If either the post-randomization value or the baseline value is missing, then the change from baseline value will also be set to missing.

Percentage change from baseline will not be calculated or presented for variables that may take 0 as a value at baseline.

3.1.4 Handling of missing data

No imputation for missing efficacy endpoints will be done. For the primary analysis, MMRM will be used and which, in the event of missing data, uses all data that are available.

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (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" (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.

In the different analyses performed, the log-transform eosinophil value can be used, a constant of 0.005 will be added to all the patients at the time of the calculation of the log eosinophil to avoid the issues due to the log-transformation.

CCI [redacted]

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

Missing ADA result at baseline data will be assumed to be negative, for other missing ADA data, no imputation is planned.

PK serum 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 serum concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. PK serum 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 NR. 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 NR.
- 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 PK serum concentration to be summarised. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

3.1.4.1 Imputation of partial missing AE dates

Date and time of AE are mandatory eCRF fields. In the rare cases of missing 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.

3.1.4.2 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 31st of December of the collected year.

3.1.4.3 Imputation of partial missing COPD history dates

Only partial COPD 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 January 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 the month is missing, then impute 31st of December of the collected year.

3.1.5 Analysis visit windows

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

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

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 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.

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- If screening and re-screening visits have same date and time then the re-screening assessment will be used in the analysis.

The visit windows will be calculated by bisecting the scheduled visit days. The lower limit of each window will be the mean of the 2 adjacent planned study days, rounded up to the nearest integer, except for the first post-treatment visit, which will start at 2. The upper limit of each window will be the mean of the 2 adjacent planned study days, rounded down to the nearest integer.

Table 7 Analysis visit windows for pre-BD clinic spirometry, physical examination, vital signs, nasal swab for SARS-CoV-2 nucleic acid test

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV5	Week 2	Visit 5, Week 2	15	All assessments on or after the first administration of investigational product to 22
SV6	Week 4	Visit 6, Week 4	29	23 to 43
SV7	Week 8	Visit 7, Week 8	57	44 to 71

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV8	Week 12	Visit 8, Week 12	85	72 to 99
SV9	Week 16	Visit 9, Week 16	113	100 to 127
SV10	Week 20	Visit 10, Week 20	141	128 to 155
SV11	Week 24	Visit 11, Week 24	169	156 to 183
SV12	Week 28	Visit 12, Week 28	197	184 to 211
SV13	Week 32	Visit 13, Week 32	225	212 to 239
SV14	Week 36	Visit 14, Week 36	253	≥240

BD = Bronchodilator; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; 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 8 Analysis visit windows for serum chemistry, haematology, coagulation (except fibrogen), CCI

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV5	Week 2	Visit 5, Week 2	15	All assessments on or after the first administration of investigational product to 22
SV6	Week 4	Visit 6, Week 4	29	23 to 57
SV8	Week 12	Visit 8, Week 12	85	58 to 113
SV10	Week 20	Visit 10, Week 20	141	114 to 169
SV12	Week 28	Visit 12, Week 28	197	170 to 211
SV13	Week 32	Visit 13, Week 32	225	212 to 239
SV14	Week 36	Visit 14, Week 36	253	≥240

SV = Study Visit.

Table 9 Analysis visit windows for immunogenicity assessments

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV5	Week 2	Visit 5, Week 2	15	Start of first administration of investigational product to 22

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV6	Week 4	Visit 6, Week 4	29	23 to 57
SV8	Week 12	Visit 8, Week 12	85	58 to 113
SV10	Week 20	Visit 10, Week 20	141	114 to 155
SV11	Week 24	Visit 11, Week 24	169	156 to 183
SV12	Week 28	Visit 12, Week 28	197	184 to 211
SV13	Week 32	Visit 13, Week 32	225	212 to 239
SV14	Week 36	Visit 14, Week 36	253	≥240

SV = Study Visit.

Table 10 Analysis visit windows for ECGs

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV8	Week 12	Visit 8, Week 12	85	All assessments on or after the first administration of investigational product to 141
SV12	Week 28	Visit 12, Week 28	197	142 to 225
SV14	Week 36	Visit 14, Week 36	253	≥226

ECG = Electrocardiogram; SV = Study Visit.

Table 11 Analysis visit windows for urinalysis and SGRQ assessments

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV6	Week 4	Visit 6, Week 4	29	All assessments on or after the first administration of investigational product to 57
SV8	Week 12	Visit 8, Week 12	85	58 to 141
SV12	Week 28	Visit 12, Week 28	197	≥142

SGRQ = St George's respiratory questionnaire; SV = Study Visit.

Table 12 **Analysis visit windows for airwave oscillometry, weight, SARS-CoV-2 serology test (serum), CCI [redacted]**

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV3	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV8	Week 12	Visit 8, Week 12	85	All assessments on or after the first administration of investigational product to 141
SV12	Week 28	Visit 12, Week 28	197	≥142

CCI [redacted]; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; CCI [redacted] SV = Study Visit.

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 16 Analysis visit windows for echocardiogram, post-BD clinic spirometry assessments CCI [redacted]

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV1	Week -5 to -4	Baseline	1	All assessments prior to the first administration of investigational product
SV8	Week 12	Visit 8, Week 12	85	2 to 141
SV12	Week 28	Visit 12, Week 28	197	≥142

SV = Study Visit.

Table 17 Analysis visit windows for cough monitoring

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV2	Week -3 to -1	Baseline	1	All assessments prior to the first administration of investigational product
SV8	Week 12	Visit 8, Week 12	85	≥2

SV = Study Visit.

Any data collected at early discontinuation and unscheduled visits will be listed and will be 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.

Daily CCI [redacted] E-RS: COPD, BCSS, cough VAS etc.) will primarily be summarised and analysed as 4-weekly averages, separately. The assessment period of visit windows will be defined in Table 18.

Table 18 Labelling of 4-weekly periods for CCI [redacted] **and eDiary variables**

4-weekly period	Label
Baseline: as defined in Section 3.1.1	Evening of Day -14 to Morning of Day 1 (Baseline)
Period 1: Evening of Day 1 – Morning of Day 29	Day 1 – 29 (Week 4)
Period 2: Evening of Day 29 – Morning of Day 57	Day 29 – 57 (Week 8)
Period 3: Evening of Day 57 – Morning of Day 85	Day 57 – 85 (Week 12)
Period 4: Evening of Day 85 – Morning of Day 113	Day 85 – 113 (Week 16)
Period 5: Evening of Day 113 – Morning of Day 141	Day 113 – 141 (Week 20)

4-weekly period	Label
Period 6: Evening of Day 141 – Morning of Day 169	Day 141 – 169 (Week 24)
Period 7: Evening of Day 169 – Morning of Day 197	Day 169 – 197 (Week 28)
Period 8: Evening of Day 197 – Morning of Day 225	Day 197 – 225 (Week 32)
Period 9: Evening of Day 225 – Morning of Day 253	Day 225 – 253 (Week 36)

For all other assessments, there will be no analysis visit windows, the data will be reported according to CRF visit.

For variables analysed using a 4-weekly period, all the days should be considered.

3.1.6 Analysis timepoints for vital signs

For reporting of analysis timepoints in vital signs summaries and listings, the next time windows will be applied:

Table 19 Vital signs timepoint labelling

Visit	Analysis Visit	Planned timepoint
Screening (SV1), SV5, Follow-up 1 (SV13), Follow-up 2 (SV14)	Baseline / Visit 5, Week 2 / Visit 13, Week 32/ Visit 14, Week 36	NA
First 2 doses of study intervention (SV3 and SV6)	Baseline / Visit Y, Week X	Pre-dose
	Visit Y, Week X	Post-dose
	Visit Y, Week X	30 min Post-dose
	Visit Y, Week X	60 min Post-dose
	Visit Y, Week X	120 min Post-dose
SV7 – SV11	Visit Y, Week X	Pre-dose
	Visit Y, Week X	Post-dose
	Visit Y, Week X	30 min Post-dose
	Visit Y, Week X	60 min Post-dose
SV12	Visit 12, Week 28	NA

NA = Not Applicable, SV = study visit.

To be noted, that assessment that was done at SV3 pre-dose will be labelled “Baseline – Pre-dose”, and the following post-dose assessments at SV3, eg Post-dose, 30 min Post-dose, will have analysis visit label “Day 1”.

In case of early discontinuation visit, if the visit falls during an on-treatment visit, the corresponding visit will be assigned for the analysis visit with Pre-dose as timepoint.

3.1.7 Study phase windows

For the purpose of the statistical analysis, the assessments will be allocated to the study phase in which they are collected as reported below.

Table 20 Study phase windows

Study phase	Phase Window for Analysis (Days)
Pre-treatment	Prior to the first administration of investigational product (day <1[a])
On-treatment	≥ day 1[b] to last dose date plus 28 days (included)
Follow-up	> last dose date plus 28 days

[a] Includes all measurements collected before first dose of IP. If the measurement is collected on day 1 it cannot be determined if it was done before or after the first dose of IP (due to missing time and/or planned time point), then it will be considered as collected after first dose of IP.

[b] Includes all measurements collected on the day of first dose of IP, at the time of IP intake and after.

3.1.8 Derivation of durations

3.1.8.1 Time since COPD diagnosis (years)

Time from COPD first diagnosis date to screening will be calculated as (date of first diagnosis of COPD minus date informed consent signed plus one) divided by 365.25. If date of first diagnosis of COPD is partially missing then imputed date will be used (Section 3.1.4.3).

3.1.8.2 Time since COPD symptoms started (years)

Time from COPD first symptoms date to screening will be calculated as (date of first symptoms of COPD minus date informed consent signed plus one) divided by 365.25. If date of first symptoms of COPD is partially missing then imputed date will be used (Section 3.1.4.3).

3.1.8.3 Time since last exacerbation (months)

Time since last COPD exacerbation date to screening will be calculated as (date of most recent exacerbation minus date informed consent signed plus one) divided by 365.25 and multiplied by 12.

3.1.8.4 CCI

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3.1.8.5 Duration of exposure (days)

Exposure duration is calculated only for participants in the As-treated population as the total number of days on study drug. Exposure is calculated as the study drug injection last date plus 28 minus study drug injection first date plus one. 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.

3.1.8.6 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.

3.1.8.7 Time from last IP administration to AE onset (days)

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

3.1.8.8 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.

3.1.8.9 Time from last IP administration to death (days)

Time from last IP administration to death will be calculated as date of death minus date of last IP administration plus one.

3.1.9 Subgroups

Analysis for the primary efficacy endpoint will be provided for the following subgroups:

- Gender (Male vs. Female)
- Age (≥ 40 – < 65; ≥ 65 – 80)
- Race (as collected in CRF)
- BMI in kg/m² (<19, ≥19 to <25, ≥25 to <30, ≥30)
- Geographic region (Eastern Europe, Western Europe and North America, Rest of the world. Note: other countries/regions may be added during the course of the study; if new countries are added, and insufficient number of participants from these countries is recruited, then they will be incorporated in the 'Rest of the world' subgroup)
- Baseline FEV_1 as percent PNV (<50% vs ≥50%)
- Maintenance medications:
  - ICS vs no ICS (as per stratification)
  - LABA/ICS vs LABA/LAMA/ICS vs LABA/LAMA
- Number of COPD exacerbations in last 12 months as collected in eCRF (≤1 vs ≥2)

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- Smoking status at baseline (current smoker vs former smoker)
- Baseline BCSS based on 14-day average (<median vs ≥median)
- Baseline total SGRQ score (<median vs ≥median)
- Extent of emphysema (< 10% vs ≥ 10%)
- SARS-CoV-2 using a nucleic acid test (positive at any point vs never positive)
- SARS-CoV-2 using a serology test (negative at baseline and positive at end of study vs negative at baseline and at end of study).

Analysis for the secondary endpoints (change from baseline through Week 28 in pre-BD and post-BD FEV_1, pre-BD and post BD FVC) by extent of emphysema (< 10% vs ≥ 10%) will be performed.

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Modality of the subgroups will only be explored if there is at least 15% of the total participants in this category.

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3.2 Baseline assessments and other participant-specific characteristics

Demographic and participant characteristics, medical history and nicotine and alcohol use are collected pre-treatment as per SoA (CSP Section 1.3).

3.2.1 Demographics and participant-specific characteristics

Demographic and participant characteristics include age, age group (≥ 40 – < 65; ≥ 65 – 80, age group for EudraCT reporting purpose (≥ 18 – < 65; ≥ 65), sex, race, ethnic group, country, height (cm), weight (kg), body mass index (kg/m²). Age is the age at screening as reported in the eCRF. BMI (kg/m²) is calculated as described in Section 3.8.3.

Height and weight will be allocated to the analysis visits as per Section 3.1.5. Only baseline values are included in the demographic and participant characteristics.

For subgroup analysis, participants will be allocated to geographical region depending on a country and site of the participation in this study:

- Eastern Europe: Hungary, Poland, Czech Republica;

- Western Europe and North America: Spain, Netherlands, United Kingdom, Germany, Denmark, Canada, United States;
- Rest of the world: Israel, South Africa, Australia, New Zealand, Taiwan.

(Note: new countries/regions may be introduced during the course of the study).

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3.2.2 Medical history

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 25.1 or higher.

3.2.3 Prior and concomitant medication

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 3.1.4 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 6.5.5. They will be defined following a physician review (prior to database lock for any study delivery) 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 (Other viral vaccines).

3.2.4 COPD history

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

- COPD first diagnosed date;
- First appearance of COPD symptoms date;
- Most recent exacerbation date;
- Number of COPD exacerbations within previous 12 months (including exacerbations resulted in antibiotic treatment, oral steroid treatment, hospitalization and total number of exacerbations);
- Number of COPD exacerbations within previous 24 months.
- Specific diagnosis of COPD (including diagnosis of chronic airway obstruction, diagnosis of emphysema, diagnosis of obstructive chronic bronchitis);
- COPD status based on GOLD Classification (including presence of chronic symptoms or respiratory failure);
- Other diagnosis of obstructive lung disease (including previous diagnosis of asthma, diagnosis of rhinitis, rhinitis seasonal or all year round).

Based on collected COPD history information, time since COPD diagnosis, time since COPD symptoms started and time since the most recent exacerbation will be calculated as described in Section 3.1.7. Partial dates will be imputes as described in Section 3.1.4.3.

COPD treatments at randomization will be collected in the eCRF as part of concomitant medication, and classified as ICS/LABA, LABA/LAMA, ICS/LABA/LAMA programmatically.

3.2.5 Substance usage

Alcoholic beverages status and consumption, and smoking status (cigarettes, cigars, pipes, smokeless tobacco and non-tobacco nicotine products) together with the consumption of cigarettes in pack-years will be collected.

CCI [redacted]

3.3 Primary and secondary efficacy variables

3.3.1 Pre-BD clinic spirometry

Change from baseline in pre-BD FEV_1 measured in clinic at Week 12 is the primary endpoint of the study. CCI [redacted]

Lung function (FEV_1 and FVC) will be measured by spirometry using equipment provided by a central vendor. Spirometry testing will be performed at specified visits according to the SoA (CSP Section 1.3). CCI [redacted]

3.3.2 Airwave Oscillometry

Change from baseline to Week 12 in AO parameters (R5-R20, R5, R20 and AX) is a secondary endpoint of this study.

AO will be performed at specified visits as detailed in the SoA (CSP Section 1.3), using the endpoints of R5-R20, R5, R20, and AX:

- Frequency dependence of Resistance, 5-20 Hz (R5-R20, measured in kPa*s/L)
- Respiratory Resistance at 5 Hz (R5, measured in kPa*s/L)
- Respiratory Resistance at 20 Hz (R20, measured in kPa*s/L)
- Area under the reactance curve (AX, measured in kPa/L)

CCI [redacted]

3.3.3 Objective cough monitoring

Daily (ie, 24 hour) cough frequency, night-time cough frequency and awake time cough frequency are secondary endpoints for the study.

Objective cough frequency over 24 hours will be measured using an ACM (VitaloJAK™; Vitalograph, Buckinghamshire, UK), which will be fitted and worn by the participants for approximately 24 hours after the visits detailed in the SoA (CSP Section 1.3). The device will record:

- Total counted cough events for the whole 24 hours;
- The total number of coughs flagged within ‘Sleep’ events;
- The total number of coughs for the full 24-hour recording minus coughs flagged within ‘Sleep’, ‘Mute’, ‘Flagged Area’, ‘Device Not Attached’ and ‘Recording Ended Early’ events, as calculated by the portal software.

Daily cough frequency as full average hourly cough of the full duration of recording, night time cough frequency as sleep average hourly cough of the duration of recording at night, and awake time cough frequency as awake average hourly cough of the full duration of recording minus sleep recording will be derived from the recording. All frequency data will be recorded to 2 decimal places. The minimum recording time for the measurement to be 'done' is one hour, however the minimum recording time required for analysis is 18 hours within the 24-hour interval, and participants' data with recording time < 18 hours will be excluded from analysis.

3.3.4 COPDCompEx events

The COPDCompEx is a composite endpoint for exacerbations in COPD. The COPDCompEx combines exacerbations with events defined from participant e-Diaries and PEF.

Note the COPDCompEx definition typically includes dropout due to lack of efficacy as a CompEx event. However, since 'lack of efficacy' is not listed as a reason for drop out in this study, we will not include the drop out criterion for COPD CompEx in this study.

A participant will be considered to have a CompEx event during the planned Intervention Period if the participant has one or more of the following:

- COPDCompEx defined exacerbation, those collected in eCRF with at least one of the following criteria met:
  - Associated Hospitalizations = Yes;
  - Systemic Corticosteroids (injected and/or oral) = Yes;
  - Antibiotics = Yes;
  - Any emergency room visit due to COPD exacerbation? = Yes.

- A diary event - An objective deterioration, which is defined as either the threshold criterion or the slope criterion (or both), being met for ≥2 consecutive days. See derivation below.

For this purpose, "2 consecutive days" means strictly the same 2 consecutive days when assessing multiple requirements within those days. For the eDiary data (which is captured twice during the day), one day will be defined by the evening/morning pairing as the other eDiary endpoints in this trial. Diary data recorded in the evening of day n and in the morning of day n+1 will belong to study day n.

Derivation of Diary Events:

The fulfilment of objective deterioration criteria will be calculated for each (single) diary variable for thresholds and slopes:

Threshold criterion:

The threshold assessment in each 2-day rolling period:

(a) ≥ 12% decrease from baseline in morning PEF.

(b) ≥ 1.75 doses increase from baseline in daily total rescue medication (one day is defined as evening/morning pairing. The number of doses of rescue medication is defined as the number of puffs of inhaler recorded in the evening and morning, respectively.) If either the evening or morning result is missing then the single non-missing result will be used.

(c) ≥ 0.75 increase from baseline or having maximal symptom score 4 in at least one of the symptom scores: breathlessness, cough, sputum. To be specific:

(i) ≥ 0.75 increase from baseline or having maximal symptom score 4 in breathlessness daily score

or

(ii) ≥ 0.75 increase from baseline or having maximal symptom score 4 in cough daily score

or

(iii) ≥ 0.75 increase from baseline or having maximal symptom score 4 in sputum daily score.

The threshold criterion is met if [(a) or (b)] and at least one of (c) are met on 2 consecutive days.

Slope criterion:

The regression slope assessment in each preceding 5-day rolling period:

(d) Morning PEF slopes ≤ -3%/day.

(e) Daily total rescue medication slope ≥ 0.4 doses/day

(f) Slope ≥ 0.2/day in all of symptom scores breathlessness, cough, sputum.

The slope criterion is met if [(d), (e) and (f)] are all met, and at least one of [(a), (b) or (c)] is met.

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the absolute values of each of the variables separately against day number, with no other variables included in the regression model.

A regression slope will be calculated provided there are at least 2 non-missing values in the required 5 days. If one or more of the variables above (d, e or f) does not have at least 2 non-missing values in the required 5 days, then the slope requirement cannot be met.

For morning PEF, the regression slope thus obtained will first also be divided by the baseline PEF value before applying the above criterion.

The following table shows how the timing for the 5-day requirement for the regression slopes fits with the 2-consecutive day requirement, where "Day 0" here refers to the first of the 2 consecutive days (shaded) to be used each time the rolling 2 consecutive day assessment is made:

Table 21 Timing for assessment of COPDCompEx slope criterion

	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1
Threshold (a), (b), (c)					x	x
Slope	x	x	x	x	x	

A diary event can occur when (i) the threshold deterioration criterion is met for at least 2 diary variables, or when (ii) the threshold deterioration criterion is met for one diary variable, and the slope criterion is fulfilled for all included variables. In case of (i), the diary event is defined to start on the first day of the 2 consecutive deterioration days (event days 0–1). Any missing data in this 2-day window will make the event missing. In case of (ii), the event is defined to start on the first of the 2 days fulfilling the threshold criterion. This means that the slopes are calculated for days -4 to 0 of an event. At least 2 days with data are needed to calculate slopes, otherwise the event is considered missing.

Start and End dates of COPDCompEx events

The start date of a CompEx event is defined as the earliest of the exacerbation or objective deterioration start dates which meets the definition. Objective deterioration start date is defined as the earliest Day 0 (in notation from Table 21) from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criterion.

The end date of a CompEx event is defined as the latest of the exacerbation or objective deterioration end dates which meets the definition. Objective deterioration end date is defined as the latest Day 1 (in notation from Table 21) from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criterion.

If the end date of the first CompEx event and the start date of the second CompEx event are less than 7 days apart for any participant, then these will be counted as one CompEx event.

For CompEx analyses, only on-treatment events (events occurring from randomization first dose of study intervention up to and including 28 days post last dose) will be considered.

3.3.4.1 Time to first COPDCompEx event

Time to first COPDCompEx event is the secondary endpoint of the study.

Time to first COPDCompEx event (days) will be calculated as: [Start date of first event or censoring – date of the first dose of study intervention+ 1].

Date of first event will be the first start date of a COPDCompEx event as defined above. For participants who do not experience an on-treatment COPDCompEx event, date of censoring will be the minimum of date of last dose plus 28 days, or last day of eDiary recording if sooner.

3.3.4.2 CCI

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3.4 Patient reported outcome variables

3.4.1 Evaluating Respiratory Symptoms in COPD (E-RS™: COPD)

Change from baseline to Week 12 in 4-weekly mean ER-S: COPD is a secondary endpoint of this study.

The E-RS™: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD. Summation of E-RS™: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0 to 17), cough and sputum (3 items; score range: 0 to 11) and chest symptoms (3 items; score range: 0 to 12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity (see Appendix B 1).

Scoring instructions:

Convert each original item response code to an item-level raw score, by matching the responses in Appendix B 1. A daily RS-Total score is derived by summing across all 11 item-level scores. Subscale scores are computed as sum of item-level scores for each subscale (domain):

- RS-Breathlessness score will be calculated as the sum of items 7, 8, 9, 10, 11.
- RS-Cough & Sputum score will be calculated as the sum of items 2, 3, 4.
- RS-Chest symptoms score will be calculated as the sum of items 1, 5, 6.

Domain and total scores will not be calculated if at least one item response is missing.

The 4-weekly mean will be calculated as the sum of all non-missing daily scores over the 28-day evaluation period, as described in Table 18, divided by the number of non-missing daily scores. The 4-weekly mean will be calculated if there are at least 14 completed days during the 28-day evaluation period, where a day = evening + following morning.

3.4.2 Cough Visual Analogue Scale

Change from baseline to Week 12 in average Cough VAS score over the previous 4 weeks is a secondary endpoint of this study.

Participants will be asked to complete a cough severity VAS (100 mm linear scale marked with a horizontal line by the participant, with 0 mm representing ‘‘no cough’’ and 100 mm representing “worst cough”) measuring subjective assessment by the participant of the prior 24 hrs for severity of cough symptoms (Smith et al 2006). The cough VAS will be completed each evening in the eDiary.

The 4-weekly mean cough VAS score will be calculated as the sum of all non-missing daily scores over the 28-day evaluation period, as described in Table 18, divided by the number of non-missing daily scores. The 4-weekly mean will be calculated if there are at least 14 completed days during the 28-day evaluation period, where a day = evening + following morning.

3.4.3 Breathlessness, Cough and Sputum Scale

Change from baseline to Week 12 in the average BCSS score over the previous 4 weeks is a secondary endpoint of this study.

The BCSS© is a 3-item daily diary that assesses the severity of the 3 symptoms: breathlessness, sputum, and cough, each on a 5-point scale (see Appendix B 4). Item scores will be reported as domains scores and are summed to yield a total score. Higher scores for each domain, and thus for total score, indicate more severe symptoms. The BCSS will be captured each evening via the eDiary.

The 4-weekly mean BCSS score will be calculated as the sum of all non-missing daily scores over the 28-day evaluation period, as described in Table 18, divided by the number of non-missing daily scores. The 4-weekly mean will be calculated if there are at least 14 completed days during the 28-day evaluation period, where a day = evening + following morning.

3.4.4 St George's Respiratory Questionnaire

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 1991). The SGRQ yields a total score and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones and Forde 2009). The principle of calculation of total score and domain scores in accordance with the abovementioned user manual are provided in Appendix B 3.

The SGRQ will be completed using the eDiary in accordance with the SoA (CSP Section 1.3), and a 4-week recall version will be used.

The key outcome variable for the SGRQ will be the change in total SGRQ score from baseline to Week 12, but the change in total score from baseline to Week 4 and Week 28 will also be derived (see Section 3.1.3). Change in the domain score from baseline to Week 4, Week 12 and Week 28 will also be derived.

Other variables based on SGRQ to report include:

- Proportion of participants with a decrease in SGRQ score of ≥ 4 points from baseline to Week 12 (Yes=1/No=0)
  - Yes: change from baseline SGRQ score to SGRQ score at Week 12: ≤ -4
  - No: change from baseline SGRQ score to SGRQ score at Week 12: > -4
- Proportion of participants with a decrease in SGRQ score of ≥ 4 points from baseline to Week 28 (Yes=1/No=0)
  - Yes: change from baseline SGRQ score to SGRQ score at Week 28: ≤ -4
  - No: change from baseline SGRQ score to SGRQ score at Week 28: > -4

Participants with missing or non-evaluable SGRQ score will be considered as not achieving SGRQ response.

3.4.5 CCI

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3.4.6 CCI

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3.4.7 COPD Assessment Test

Participants will be asked to complete a CAT at SV1. The CAT is designed to measure the impact of COPD on a person's life (Jones et al 2009). The CAT consists of eight questions that ask the participant to rate items relating to symptoms and impact on quality of life (such as normal activity and sleep). Each question is performed on a scale from 0 to 5 with 0 being the best possible health status or least impairment and 5 being the worst health status or greatest impairment.

The CAT total score is calculated by summing the scores from each question. The CAT total score has a range from 0 to 40, with higher score denoting a more severe COPD impact on participant's life. A score will not be calculated if at least one response is missing.

3.5 Pharmacokinetic variables

Serum samples will be collected for measurement of serum concentrations of MEDI3506 as specified in the SoA in CSP Section 1.3.

3.6 Immunogenicity variables

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by, or on behalf of, AstraZeneca, using an appropriately validated bioanalytical method. Tiered analyses will be performed to include screening, confirmatory, and titer assay components.

3.6.1 ADA definitions

ADA detection at participant level:

- A participant is considered ADA positive if a collected sample is tested positive at any time during the study, including baseline and/or post-baseline (see definition for ADA prevalence below).
- A participant is considered ADA negative if collected samples are tested negative at all timepoints, including baseline and post-baseline.

The proportion of ADA-positive participants in a population is known as ADA prevalence.

Treatment-related ADA development at participant level:

Treatment-emergent ADA positive (TE-ADA+) is defined as the sum of:

- Treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive) and
- Treatment-boosted ADA positive (ADA positive at baseline and boosted (≥4 fold) the pre-existing titre during the study period).

Non-Treatment-emergent ADA positive (non-TE-ADA+) is defined as ADA positive but not fulfilling the definition of TE-ADA positive.

ADA incidence is the proportion of TE-ADA+ participants in a population.

ADA persistently positive is defined as ADA negative at baseline and positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or ADA positive at last post-baseline assessment. ADA transiently positive is defined as ADA negative at baseline and at least one post- baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

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

3.6.2 Categories of ADA responses

Numbers and proportions of:

- Participants who are ADA positive at any time during the study, including baseline and/or post-baseline (also generally referred to as ADA positive).
- Participants who are ADA negative at all assessments, including baseline and post-baseline (also generally referred to as ADA negative).
- Participants who are ADA positive at baseline only.
- Participants who are ADA positive at baseline and at least one post-baseline assessment.
- Participants who are treatment-emergent ADA positive (see definition in Section 3.6.1), reported overall and separately as treatment-induced and treatment-boosted participants.
- Participants who are non treatment-emergent ADA positive (see definition in Section 3.6.1).
- Participants who are persistently ADA positive, which is defined in Section 3.6.1.
- Participants who are transiently ADA positive, defined in Section 3.6.1.
- Participants who are ADA positive with maximum titre > median of maximum titres.

3.7 Exposure to study intervention

Duration of exposure

Exposure duration (days) is calculated only for participants in the As-treated population as the total number of days on study drug. Exposure is calculated as (the study drug application last date plus 28 days) minus study drug application first date plus one. 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.

Number of doses received

Full dose of study drug is administered in 2 injections. The date and time of the first injection will be recorded in eCRF.

Total number of doses received will be calculated as number of study visits where at least one injection with dose level >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 SV11 dose.

Treatment interruptions

Study intervention is interrupted when at least one of the following events occur:

- Checkbox with action taken with study intervention = "Drug Interrupted" is ticked on EX eCRF;
- There is no dosing (dose recorded as '0' in eCRF) however visit has been performed;
- There is a dose < 4 ml recorded in eCRF (only one syringe has been administered or the volume of 2 syringes is less than intended);
- There are less than 4 kits dispensed and less than 4 kit numbers recorded in eCRF.

Permanent drug withdrawal is not considered an interruption.

3.8 Safety outcome variables

The following safety data will be collected:

- AEs, SAEs, AESI;
- Vital signs;
- Clinical chemistry, haematology, and urinalysis;
- ECGs;
- LVEF as measured by echocardiogram;
- NT-proBNP;
- SARS-CoV-2 tests.

3.8.1 Adverse events

Adverse events and SAEs on this study will be collected from informed consent throughout the intervention period and including the follow-up period. AEs will be coded with MedDRA version 25.1 or higher.

AE data will be allocated to the study phase (as defined in section 3.1.7) according to their onset date.

AEs will be defined as treatment emergent adverse events (TEAEs) if they have an onset, during the on-treatment phase. AEs with a missing start date will be considered as on-treatment.

Adverse events of special interest

The following AESIs will be particularly monitored in this study:

- Hepatic function abnormality meeting the definition of HL as described in CSP Section 8.3.7.
- Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions), for example anaphylaxis and severe allergic reactions, and immune complex disease.
- Injection site reactions (ISR).
- Cardiac events (including angina or myocardial infarction, congestive heart failure, symptomatic atherosclerotic vascular disease, cor pulmonale, or arrhythmia).
- Serious infections (including opportunistic infections and viral reactivations), for example herpes simplex virus/varicella zoster virus, Epstein Barr virus/cytomegalovirus, TB, and all other opportunistic infections listed in the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents: Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America (NIH 2019).
- Gastrointestinal AEs
- Malignancy

AEs will be assigned to a specific category based on investigator's judgement, using a checkbox on the AE CRF page. In addition, standardized MedDRA queries (SMQs) will be used when possible, and a selection of HLTs, SOCs and/or PTs will be used to represent other situations, to perform a cross-check with eCRF categories. A comprehensive list will be provided by the patient safety team prior to any study delivery.

COVID-19 related AEs and SAEs

AE or SAE will be considered as related to COVID-19 if a participant has been tested positive for SARS-CoV-2 (by nucleic acid or serology test), during the intervention and follow-up periods and had an AE or SAE associated with COVID-19 based on the COVID-19 SMQ.

3.8.2 Laboratory variables

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

Table 22 Laboratory Safety Variables

Haematology/haemostasis (whole blood[a])	**Clinical chemistry (serum)**
B-Haemoglobin (Hb)	S-Creatinine
B-Leukocyte count	S-Bilirubin, total
B-Leukocyte differential count (absolute count)	S-ALP
B-Platelet count	S-AST
B-Haematocrit	S-ALT
B-Red blood cell count (RBC)	S-Albumin
Urinalysis	S-Potassium
U-Appearance and Color	S-Sodium
U-Specific gravity	S-GGT
U-Hb/Erythrocytes/Blood	S-Blood urea nitrogen
U-Glucose	S-Total Protein
U-Ketones	S-HbA1c
U-pH	S-NT-ProBNP
U-Bilirubin	S-Tryptase (only to be taken in event of suspected anaphylaxis see CSP Appendix I)
U-Leukocytes	CCI [redacted]
U-Protein	
Microscopy including white blood cell/RBC and casts	
Pregnancy test (dipstick- urine human chorionic gonadotropin) as per SoA; NOTE: additional timepoint for female participants of CT sub-study	
Coagulation	
CCI [redacted]	Activated partial thromboplastin time (APTT)
Prothrombin International normalised ratio (INR)	Prothrombin Time

[a] Whole blood samples will be collected concurrently for both haematology CCI [redacted] CCI [redacted].

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; AST = Aspartate aminotransferase; B = Blood; CCI [redacted] FSH = Follicle stimulating hormone; GGT = Gamma-glutamyl transferase; Hb = Hemoglobin; HbA1c = Hemoglobin A1c; NT-ProBNP = N-terminal pro-brain natriuretic peptide; RBC = Red blood cells; S = Serum; SoA = Schedule of activities; U = Urine.

Additionally, other safety tests will be performed (details in Section 3.8.6).

3.8.3 Vital signs

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

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

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), high (if value is above the upper limit), and high change (if increase from baseline is greater than prespecified criterion) and low change (if decrease from baseline is greater than prespecified criterion) according to the following normal reference ranges:

Table 23 Vital sign reference ranges

Parameter	Standard Unit	Lower limit	Upper limit	Change Criteria
Body temperature (oral, tympanic)	°C		>37	±1
DBP	mmHg	<60	>100	±15
SBP	mmHg	<90	>160	±30
Heart (pulse) rate	beats/min	<50	>100	±20
Respiratory rate	breath/min	<12	>24	±4

DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure.

High value (H) is defined as upper reference limit. High change (HC) is defined as increase from baseline greater than prespecified criterion. Low value (L) is defined as below lower reference limit. Low change (LC) is defined as decrease from baseline greater than prespecified criterion.

3.8.4 Electrocardiogram

Electrocardiograms will be performed at timelines as specified in the SoA. Electrocardiogram variables will be collected, as follows:

- Heart rate (beats/min);
- RR interval (msec);
- QRS interval (msec);

- PR interval (msec);
- QT interval (msec).

Additionally, QTc interval corrected for heart rate will be calculated directly from the CRF for Fridericia's correction and derived for Bazett's correction using

Fridericia's correction: $QTcF[msec] = QT[msec]/(RR[sec]^{1/3})$

Bazett's correction: $QTcB[msec] = QT[msec]/(RR[sec]^{1/2})$

At baseline, pre-dose of study intervention at SV3 (Day 1), triplicate ECGs will be performed (all 3 ECGs within a 5-minute time period, at least 1 minute apart). Electrocardiograms taken at all other times will be single assessments. 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 24).

Table 24 ECG normal reference ranges

Parameter (standard unit)	Lower limit	Upper limit	Change criteria
Heart rate (beats/min)	<60	>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	+30
QTcB (msec)	N/A	>450	+30
QTcF (msec)	N/A	>450	+30

3.8.5 Echocardiogram

A transthoracic echocardiogram to assess LVEF will be performed at timelines as specified in SoA (CSP Section 1.3).

3.8.6 Other safety variables

NT-proBNP

NT-proBNP samples will be collected at SV1, SV8, SV12 and at Early discontinuation visit.

SARS-CoV-2 nucleic acid test

Nasal swab for SARS-CoV-2 nucleic acid test will be performed at SV1, SV2, SV3, SV5-SV14, E/D visit and at any point after for a participant suspected of having COVID-19.

SARS-CoV-2 serology test

SARS-CoV-2 serology test will be performed at SV3, SV8, SV12 and at Early discontinuation visit.

3.9 CCI

3.9.1 CCI

CCI

CCI

3.9.2 CCI

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3.9.3 CCI

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3.9.3.1 CCI

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3.9.3.2 CCI

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3.9.3.3 CCI

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3.9.4 CCI

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3.9.5 CCI

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3.9.7 CCI

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CCI [redacted]

CCI [redacted]

CCI [redacted]

4 ANALYSIS METHODS

There are three planned analyses for this study:

Primary Analysis

The Primary Analysis will occur once all participants have either completed the Week 12 assessments or withdrawn from the study. The Primary Analysis will include all data captured during 12-week double-blind intervention period, defined as the period between randomization visit (Visit 4) and Week 12 visit (Visit 8). This will include all available data from all visits up to and including Week 12, irrespective of whether the participant discontinued study intervention or received reliever therapy. The statistical analysis will compare CCI [redacted] of MEDI3506 to Placebo. Personnel from AstraZeneca or its representatives directly associated with the conduct of this study will be unblinded at the Primary Analysis. Personnel from the study sites, and the study participants, will remain blinded until the completion of the Final Analysis.

End of Treatment analysis

The End of Treatment analysis will occur once all participants have either completed the Week 28 assessments or withdrawn from the study. This will include all available data from all visits up to and including Week 28, irrespective of whether the participant discontinued study intervention or received reliever therapy. The statistical analysis will compare CCI [redacted] of MEDI3506 to Placebo.

Final Analysis

The Final Analysis will occur when all participants have completed the safety follow up period.

4.1 General principles

Efficacy analyses will be performed using the ITT population. Demography and baseline characteristics will be summarised by study intervention group for the ITT population.

Study intervention groups will be displayed as follow:

- MEDI3506 CCI
- 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. If n less than 3, the mean, SD, median, Q1 and Q3 will not be reported. 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<lower limit of quantification, 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.
- In case the original value is reported for 3 or more decimals, then number of decimal places presented in the displays will be limited to 3 decimal places for every statistic.
- For categorical data, percentages will be rounded to 1 decimal place.
- Original data should be display in the listing, the derived values will be displayed with 1 additional decimal place compared to the original data.
- SAS® version 9.3 (as a minimum) will be used for all analyses.

At the time of both, the primary and the end of treatment analyses, all data collected on and prior to data cut-off dates (i.e. respectively Week 12 and Week 28 visit dates for the last subjects) will be cleaned. For the purpose of the statistical analysis, data cut-off rules might be implemented and described in a separate document. All data collected until the time of the final DBL will be included in the final analysis. No cut-off rules will be implemented for the final analysis.

For subjects whose IXRS strata does not match with data collected on the CRF, the IXRS strata will be used in the analyses

4.1.1 Statistical hypotheses

The primary efficacy endpoint is the change from baseline in pre-BD FEV_1 at Week 12. A treatment policy estimand will be applied whereby all available data are included in the analysis, irrespective of whether a participant remains on study intervention or not.

The null hypothesis is that the change from baseline in FEV_1 at Week 12 on MEDI3506 is equal to the change from baseline in FEV_1 at Week 12 on placebo. The alternative hypothesis is that the change from baseline in FEV_1 at Week 12 on MEDI3506 is greater than the change from baseline in FEV_1 at Week 12 on placebo, ie:

H_0: Change from Baseline in FEV_1 at Week 12 (MEDI3506-placebo) = 0.

H_A: Change from Baseline in FEV_1 at Week 12 (MEDI3506-placebo) > 0.

Hypothesis testing will be performed at the one-sided 10% level. If the p-value is < 0.1, reject H_0 and accept H_A.

The primary analysis will act as a gate-keeper for hypothesis testing of secondary endpoints. Should the primary analysis hypothesis H_0 be rejected, then multiplicity will be controlled for a subset of key secondary endpoints using the Hochberg procedure.

Hypothesis testing of secondary endpoints

To account for multiplicity to test the primary endpoint (change from baseline in pre-BD FEV_1 at Week 12) and key secondary endpoints, the Hochberg procedure will be used to control the overall type I error rate.

Let H_0 denote a null hypothesis as stated above, and H_1, H_2, H_3, H_4 denote null hypotheses tested on key secondary endpoints:

H_1: Difference in time to first COPDCompEx event at Week 28 (MEDI3506-placebo) = 0.

H_2: Change from Baseline in daily cough frequency at Week 12 (MEDI3506-placebo) = 0.

H_3: Change from Baseline in R5-R20 at Week 12 (MEDI3506-placebo) = 0.

H_4: Change from Baseline in mean BCSS score (over the previous 4 weeks) at Week 12 (MEDI3506-placebo) = 0.

Let p_i denote the p-value for the hypothesis H_i, where $i = 1\ldots4$. Let $p_{(1)}$, $p_{(2)}$, $p_{(3)}$, $p_{(4)}$ denote ordered p-values starting from the largest, and the ordered hypotheses $H_{(1)}$, $H_{(2)}$, $H_{(3)}$, $H_{(4)}$ corresponding to them.

The testing strategy will be as following:

The procedure begins with testing of the H_0 null hypothesis is tested at the full alpha level of 0.1. If the one-sided p-value is less than 0.1, then null hypothesis will be rejected, and the procedure go to Step 1.

- Step 1. The largest p-value $p_{(1)}$ is compared to its alpha critical value, $\alpha_1 = 0.1$. If $p_{(1)} > \alpha_1$, then accept and declare non-significant the hypothesis $H_{(1)}$ and go to the Step 2. Otherwise testing stops and all remaining hypotheses are rejected and declared significant.
- Step 2. Calculate new $\alpha_2 = 0.1/2$. If $p_{(2)} > \alpha_2$, then accept and declare non-significant the hypothesis $H_{(2)}$ and go to the Step 3. Otherwise testing stops and all remaining hypotheses (which have smaller p-values) are rejected and declared significant.
- Step 3. Calculate new $\alpha_3 = 0.1/3$. If $p_{(3)} > \alpha_3$, then accept and declare non-significant the hypothesis $H_{(3)}$ and go to the Step 4. Otherwise testing stops and all remaining hypotheses (which have smaller p-values) are rejected and declared significant.
- Step 4. Reject $H_{(4)}$ if $p_{(4)} \leq 0.1/4$.

The Hochberg procedure is available in PROC MULTTEST (specifying the HOCHBERG option).

4.1.2 Repeated measures mixed effects analysis of covariance model

The repeated measures mixed effects analysis of covariance model (MMRM) will be used to fit change from baseline for continuous endpoints at each visit, for the ITT population. For Primary Analysis, the model will include all available data from all visits up to and including Week 12, irrespective of whether the participant discontinued study intervention. Since a repeated measures model is being applied, no imputation will be made for missing data. The model will include fixed effects for baseline, log-transformed eosinophil value, background medication strata, geographical region, number of exacerbations during the previous 12 months (≤1 vs 2 or more), 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 between observations on a participant between visits, and Kenward-Roger correction will be used for degrees of freedom approximation in the generation of model. In

the event that the model with unstructured covariance matrix fails to converge, and alternative such as autoregressive or compound symmetry will be used instead. Estimates of the least square mean change from baseline in FEV_1 for each study intervention, and the difference between them (MEDI3506-placebo), together with two-sided 80% CI, will be obtained from the model for each visit. The significance of the study intervention effect will be tested at a 10% one-sided level of significance.

The reportable results from the model will be:

- The least-square means (LSMeans) change from baseline at each visit and their standard errors for each study intervention group
- The difference in change from baseline at certain visit between MEDI3506 and placebo (LSMeans difference) together with its two-sided 80% confidence interval (CI)
- The one-sided p-value for the difference in change from baseline at each visit between MEDI3506 and placebo

If the parameter is log-normally distributed, the variable fitted in the model will be the change from baseline in logarithmical scale, with the logarithm of the baseline value as a covariate. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

The MMRM will be as described above but the reportable results from the model will be:

- Back transformed LSmeans for each group, which correspond to the estimated ratio to baseline; back transformed LSmeans is derived as EXP(LSMean);
- The two-sided 80% CI of the back transformed LSmeans for each group; 80% CI of the back transformed LSmeans is derived as EXP(Lower limit of the 80% CI of the LSmean); EXP(Upper limit of the 80% CI of the LSmean);
- The ratio between MEDI3506 and placebo; the ratio is calculated as EXP(LSMean difference);
- The two-sided 80% CI of the ratio; the 80% CI of the ratio is calculated as EXP(Lower limit of the 80% CI of the LSmean difference); EXP(Upper limit of the 80% CI of the LSmean difference);
- One-sided p-value.

Note that a ratio lower than 1 means that the active study intervention group shows a higher decrease (or a lower increase) compared to the placebo group. On the other hand, a ratio greater than 1 means that the active study intervention group shows a lower decrease (or a higher increase) compared to the placebo group.

4.1.3 Analysis of covariance

The ANCOVA model will be used to fit change from baseline for continuous endpoints collected at only one post-baseline visit. Data used in the model are data from baseline and the scheduled tested visit. The study intervention, log-transformed eosinophil value, background medication strata, geographical region and number of exacerbations during the previous 12 months (≤1 vs 2 or more) will be considered as fixed effects of the model while the baseline value as covariate. Comparisons of MEDI3506 CCI 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; one-sided difference test, with alpha level at 10% will be used for the comparisons and for the t-type confidence interval calculation. No imputation will be made for missing data.

The reportable results from the model will be:

- The LSmeans and their standard errors for each study intervention group;
- The difference between MEDI3506 and placebo (LSmean difference) together with its two-sided 80% CI;
- The one-sided p-value for the difference between MEDI3506 and placebo.

If the parameter is log-normally distributed, the variable fitted in the model will be the change from baseline in logarithmical scale, with the logarithm of the baseline value as a covariate. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

The ANCOVA will be as described above but the reportable results from the model will be:

- Back transformed LSmeans for each group, which correspond to the estimated ratio to baseline; back transformed LSmeans is derived as EXP(LSMean);
- The two-sided 80% CI of the back transformed LSmeans for each group; 80% CI of the back transformed LSmeans is derived as EXP(Lower limit of the 80% CI of the LSmean); EXP(Upper limit of the 80% CI of the LSmean);
- The ratio between MEDI3506 and placebo; the ratio is calculated as EXP(LSMean difference);
- The two-sided 80% CI of the ratio; the 80% CI of the ratio is calculated as EXP(Lower limit of the 80% CI of the LSmean difference); EXP(Upper limit of the 80% CI of the LSmean difference);
- One-sided p-value.

4.1.4 CCI

CCI

4.1.5 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 COPD CompEx event or CCI 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, log-transformed eosinophil value, background medication strata, geographical region and number of exacerbations during the previous 12 months (≤1 vs 2 or more) 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 80% CI, and one-sided p-value for the rate ratio will be presented. The estimate of the negative binomial overdispersion parameter will also be reported.

4.1.6 Cox proportional hazards

Time to first COPDCompEx event CCI will be analysed using a Cox proportional hazard model, with study intervention, log-transformed eosinophil value, background medication strata, geographical region and number of exacerbations during the previous 12 months (≤1 vs 2 or more) fitted as covariates. Results of these analyses will be summarised as hazard ratios, two-sided 80% CI and one-sided p-values.

Time to first COPDCompEx event CCI will be displayed graphically using a Kaplan-Meier plot.

4.2 Analysis methods

4.2.1 Disposition of participants

Participants dispositions (number and percentage of participants enrolled, participants randomized, participants not randomized (incl. reasons), participants who received at least one

dose of study IP, participants who did not receive treatment, participants who completed the treatment, participants who did not complete treatment (incl. reasons), participants who completed the study and participants 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 be also provided for all discontinued participants and participants completing the study. Both, the table and the listings will be based on 'All Subjects' population (Section 2.1), and the summary will be repeated for participants in the ITT population.

The number of participants belonging to each analysis population will be presented in a summary table for each study intervention group and overall. The table will be based on 'All Subjects' population. The number and percentage of participants enrolled, completed and discontinued from the CCI will be presented by study intervention group and overall for the ITT population. Listing of all participants excluded from the any population will be also provided. The listing will include reason for exclusion from respective population and will be based on 'All Subjects' population.

For stratification factors (baseline blood eosinophils CCI and background medication (includes ICS vs does not include ICS), the number and percentage of participants in each category will be summarised by study intervention group and overall.

The number and percentages of participants remaining on treatment, discontinued treatment but continuing study, and participants withdrawn from study at each scheduled visit will be summarised by study intervention group and overall for the ITT population.

The number and percentage of participants with one or more disruption due to COVID-19 pandemic will be presented by study intervention group and overall. A listing of all participants affected by the COVID-19 related study disruption and a description of how the individual's participation was altered, will be produced. 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 administration or location was impacted by global/country situation; who performed a study drug administration);
- Concomitant medication related (if when treatment was stopped due to any global/country related situations i.e.: epidemic/pandemic, healthcare crisis etc.);
- Withdrawal from study (if primary reason for ending study is related to global/country situation).

Randomization scheme and codes as well as subjects receiving the various batch of investigational product will also be listed for all randomized subjects.

4.2.2 Important protocol deviations

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 be also listed for all participants included in the ITT 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.

4.2.3 Baseline assessments and other participant-specific characteristics

4.2.3.1 Demographics and participant-specific characteristics

All demographic and participant-specific characteristics reported in section 3.2.1 will be presented in summary tables for each study intervention group and overall; age, height, weight and BMI will be summarised descriptively. Only the baseline measurement for height, weight and BMI will be considered. All the other demographic and participant-specific characteristics will be summarised as categorical variables with the number and percentages of participants by categories. Participants recruitment by geographical region and country will be summarised.

All demographic and participant-specific characteristics will be also provided in listings. The tables and the listings will be based on the ITT population.

4.2.3.2 Medical history

Medical history as described in section 3.2.2 will be presented in summary tables as number and percentages 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 ITT population.

4.2.3.3 Prior and concomitant medication

The number and percentage of participants receiving prior or concomitant medication (by ATC4 classification system codes and generic name) will be presented by treatment in separate tables for the ITT population.

A separate table will be presented for participants who take disallowed prior or concomitant medications. Percentages will be calculated relative to the number of participants in the ITT population.

All medications will also be listed by participant for the ITT population.

4.2.3.4 COPD history

COPD characteristics at baseline (time since COPD diagnosis; time since COPD symptoms started; time since last COPD exacerbation; total number of COPD exacerbations within previous 12 months prior to screening, including exacerbations resulted in antibiotic treatment, oral steroid treatment, hospitalization; total number of COPD exacerbations within previous 24 months prior to screening; specific diagnosis of COPD, including diagnosis of chronic airway obstruction, diagnosis of emphysema, diagnosis of obstructive chronic bronchitis; COPD status based on GOLD Classification, including presence of chronic symptoms or respiratory failure; other diagnosis of obstructive lung disease, including previous diagnosis of asthma, diagnosis of rhinitis, rhinitis seasonal or all year round) and the CAT score at baseline will be summarised by treatment for the ITT population.

Descriptive summary statistics will be produced for COPD treatments at randomization such as ICS/LABA, LABA/LAMA, ICS/LABA/LAMA.

4.2.3.5 Substance usage

Summary statistics will be produced by study intervention group and overall, for substances use for the ITT population.

CCI [redacted]

4.2.4 Analysis of primary efficacy endpoint

4.2.4.1 Primary analysis of the primary endpoint

The primary efficacy endpoint is the change from baseline in pre-BD FEV_1 at Week 12. The primary estimand is a 'Treatment Policy' estimand, as follows: The difference in mean change from baseline in FEV_1 at Week 12 (MEDI3506 – placebo) will be estimated using a repeated measures mixed effects analysis of covariance model (see Section 4.1.2), for the ITT population. This will include all available data from all visits up to and including Week 12, irrespective of whether the participant discontinued study intervention or received reliever therapy. Graphical representations of the LSMeans change from baseline and the two-sided 80% CI over time will be provided by study intervention group using the ITT population.

4.2.4.2 Supportive analysis of the primary endpoint

As a supportive analysis of the primary endpoint, the MMRM analysis (see Section 4.1.2) will be repeated on the ITT population using data from visits up to and including Week 12, but excluding the data from visits after IP discontinuation. Graphical representations of the LSMeans change from baseline and the two-sided 80% CI over time will be provided by study intervention group using the ITT population.

4.2.4.3 Sensitivity analysis of the primary endpoint

As a sensitivity analysis of the primary endpoint, two MMRM analyses (see Section 4.1.2) will be performed on the ITT population: one with eosinophil strata instead of log-transformed eosinophil value and another excluding eosinophils from the fixed effect.

Additionally, a sensitivity analysis will be performed excluding data where the Spirometry Vendor have identified the results to be 'implausible'. The definition of 'implausible' will be documented separately prior to database lock.

4.2.4.4 Subgroup analysis for the primary endpoint

For each of the subgroup factors (see Section 3.1.9) a separate MMRM will be fitted using the same covariates as described for the primary analysis in Section 4.2.4.1. Background medication strata will not be a covariate if background medication strata is the subgroup; geographical region will not be a covariate if it is the subgroup; number of COPD exacerbations in last 12 months will not be a covariate if it is the subgroup. Graphical representations of the LSMeans change from baseline and the two-sided 80% CI over time will be provided for each subgroup by study intervention group using the ITT population. A forest plot (displaying the difference in mean change from baseline in FEV_1 at Week 12, together with the two-sided 80% CI and reference line at zero) will be produced for all subgroups.

4.2.4.5 Secondary analysis of the primary endpoint

The secondary analysis of the primary endpoint will consist of repeating the MMRM analysis (see Section 4.1.2) on the ITT population from visits up to and including Week 36.

The observed values and absolute change from baseline though Week 36 will be summarised.

Graphical representations of the LSMeans change from baseline and the two-sided 80% CI over time will be provided by study intervention group using the ITT population.

4.2.5 Secondary outcome variables

4.2.5.1 Time to first COPDCompEx event

Time to first COPDCompEx event based on the period from baseline to 4 weeks after last dose (Week 28) will be analysed using a Cox proportional hazard model, as described in Section 4.1.6. The data will also be displayed in a Kaplan-Meier plot.

CCI [redacted]

COPDCompEx event data, including date of event and time from the first study intervention administration to event, will be listed by participant for the ITT population, as well as the details of each criteria leading to COPDCompEx event.

4.2.5.2 Analysis of E-RS: COPD score

CCI [redacted]

Change from baseline to Week 12 in E-RS:COPD (total and domain scores) over the previous 4 weeks will be analysed using a repeated measures mixed effects analysis of covariance model as described in Section 4.1.2. CCI [redacted]

CCI [redacted] For primary analysis, LSMean change from baseline through Week 12 in E-RS:COPD total and domain scores will be presented.

A listing including mean results from each of the domain and the mean total E-RS: COPD score will be produced for the ITT population.

4.2.5.3 Analysis of BCSS score

CCI [redacted]

Change from baseline to Week 12 in mean BCSS score over the previous 4 weeks will be analysed using a repeated measures mixed effects analysis of covariance model as described in Section 4.1.2. CCI [redacted]

CCI [redacted]

CCI [redacted] For primary analysis, LSMean change from baseline through Week 12 in BCSS total and domain scores will be presented.

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

4.2.5.4 Analysis of Cough VAS score

CCI [redacted]

Change from baseline to Week 12 in cough VAS average score over the previous 4 weeks will be analysed using a repeated measures mixed effects analysis of covariance model as described in Section 4.1.2. CCI [redacted]

CCI [redacted] For primary analysis, LSMean change from baseline through Week 12 in cough VAS average score will be presented.

A listing including average cough VAS score results will be produced for the ITT population.

4.2.5.5 Analysis of SGRQ domain and total score

CCI [redacted]

Change from baseline to Week 12 in SGRQ total and domain scores will be analysed using MMRM (see Section 4.1.2). CCI [redacted]

CCI [redacted] For primary analysis, LSMean change from baseline to Week 12 in SGRQ total and domain scores will be presented.

Number and proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 12 (as defined in Section 3.4.4) will be summarised and analysed using chi-squared test as described in Section 4.1.4 for the ITT population. CCI [redacted]

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

4.2.5.6 Analysis of AO parameters

Observed values and absolute change from baseline to Week 12 CCI [redacted] in AO parameters will be summarised by visit for ITT population.

Change from baseline in AO parameters at Week 12 will be analysed using an analysis of covariance model (see Section 4.1.3). CCI [redacted]

CCI

CCI

For primary analysis, LSMean change from baseline to Week 12 in AO parameters will be presented.

AO parameters will be also reported in a listing.

4.2.5.7 Analysis of objective cough measurements

Observed values and absolute change from baseline to Week 12 in objective cough parameters will be summarised for ITT population.

Relative change from baseline in objective cough measures at Week 12 will be analysed using an analysis of covariance model as described in Section 4.1.3. Objective cough measurements will be log-transformed prior to analysis.

Arithmetic mean together with SEM of daily, night-time and awake time cough frequencies will be plotted for Baseline and Week 12 timepoints.

Cough parameters will be also reported in a listing.

4.2.6 Pharmacokinetics

Serum MEDI3506 concentrations will be summarised using descriptive statistics at each visit by study intervention group and will be listed for each participant from the PK population. Geometric mean (together with CV%) serum MEDI3506 concentration over time will be plotted. Individual serum MEDI3506 concentration over time plots will be provided.

Serum MEDI3506 concentrations by ADA category (TE-ADA negative, TE-ADA positive, ADA negative) will be summarised using descriptive statistics at each visit by study intervention group for the PK population. Spaghetti plots of individual serum MEDI3506 concentrations over time by ADA category (non TE-ADA positive, TE-ADA positive, ADA negative) will be provided.

4.2.7 Immunogenicity

Summary of ADA responses during the study with number and percentage of participants in each category (defined in Section 3.6.2) will be provided by study intervention group. Summary of AEs by ADA status (TE-ADA positive, Non-TE-ADA positive, ADA negative, ADA persistently positive and TE-ADA positive with maximum titre > median of maximum titres) will be provided. ADA results will be listed, and a listing with key information on ADA positive participants will be provided.

If there is a high incidence of ADA, the association of ADA with MEDI3506 concentration will be assessed. In addition, the relationship between ADA and efficacy may be evaluated.

4.2.8 Exploratory endpoints

4.2.8.1

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4.2.8.2

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4.2.8.3

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4.2.8.4 CCI

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4.2.8.5 CCI

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4.2.8.6 CCI

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4.2.8.7 CCI

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4.2.8.8 CCI

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4.2.8.9 CCI

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4.2.8.10 CCI

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4.2.8.11 CCI

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4.2.8.12 CCI

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4.2.9 Exposure

Duration of exposure as calculated in Section 3.1.7.5 will be summarised by study intervention groups for the As-treated population.

Number and percentages of participants receiving:

- 1 or more doses;
- 2 or more doses;
- 3 or more doses;
- 4 or more doses;
- 5 or more doses;
- 6 or more doses;
- 7 doses

will be summarised by study intervention group for the As-treated population. Additionally, the number of doses received will be summarised using descriptive statistics of mean, median, upper and lower quartiles.

Number and percentage of participants who received initial dose, who had no interruption, who had any interruption or 1, 2, 3, etc. interruption will be summarised by study intervention group for the As-treated population.

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

4.2.10 Safety data

4.2.10.1 Adverse events

All AE summary tables and listings will be created by study intervention group for the As-treated population, unless otherwise specified. AEs occurred during study intervention and follow-up period (both periods are defined in section 3.1.7) will be reported in summary tables. All AEs, including AEs for enrolled but not randomized participants and for participants who were not exposed to treatment, will be listed.

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

- Any AEs
- Any AE with toxicity grade 4 or 5
- Any AEs with outcome = death
- Any SAEs (including events with outcome = death)
- Any AEs leading to discontinuation of IP
- Any AEs leading to dose interruption
- Any AEs leading to withdrawal from study
- Any AESI

Number and percentage of participants with at least one AE by SOC term will be produced by study intervention group.

Number and percentage of participants with AE by SOC and PT term will be summarised by study intervention group. Total number of AEs by SOC and PT term will be summarised by study intervention group.

The number and percentages of participants with AEs occurring in >5% of participants in Total study intervention group will be summarised by PT and study intervention group. Non-serious adverse events occurring in greater than 5% of participants (including number and percentages of participants and number of events) in any study intervention group by SOC and PT term will be summarised by study intervention group.

The number and percentages of participants with AEs by maximum reported toxicity grade by PT term will be summarised by study intervention group.

The number and percentages of participants with AEs by relationship as assessed by investigator will be summarised by PT term and study intervention group.

Number and percentage of participants with AE leading to dose interruption of IP by SOC and PT term will be summarised by study intervention group.

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

- Study intervention group
- Participant identifier
- Sex
- Age (years)
- Event term as reported by the investigator
- PT term
- Time from first IP administration to onset of AE (days) as derived in Section 3.1.8.6
- Treatment period
- Time from last IP administration to death (days) as derived in Section 3.1.8.8
- Time from first IP administration to death (days) as derived in Section 3.1.8.9
- Received treatment for AE
- Reasonable possibility AE caused by IP

The number of SAEs by SOC and PT term will be summarised by study intervention group. The number and percentages of participants with SAEs by SOC and PT term will be summarised by study intervention group. Key participant information for participants experienced SAEs will be produced using following information:

- Study intervention group
- Participant identifier
- Sex
- Age (years)
- Event term as reported by the investigator
- PT term
- Time from first IP administration to onset of AE (days) as derived in Section 3.1.8.6

- Time from last IP administration prior to AE start date, calculated for AEs starting after the discontinuation of the IP.
- Time from start of IP administration to becoming serious
- Outcome
- Action taken with IP
- Reasonable AE caused by IP

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

- Study intervention group
- Participant identifier
- Sex
- Age
- AE as reported by the investigator
- PT term
- Time from first IP administration to AE onset
- Time from first IP administration to discontinuation of IP
- Seriousness
- Outcome
- Reasonable possibility AE caused by IP

Number and percentage of participants with AE of special interest by maximum reported toxicity grade will be summarised by study intervention group. A list of PT terms for AEs of special interest will be produced. Number of participants with AE for each medical concept (injection site reaction (ISR), serious hypersensitivity, serious infection, progression of heart failure, gastrointestinal adverse reactions, COVID-19) by maximum reported toxicity grade will be summarised by study intervention group.

Number of subjects with COVID-19 related AEs of special interest by SOC and PT will be summarised by treatment group and for total MEDI3506. Similar table will be repeated for the number of subjects with COVID-19 related serious AEs of special interest.

All AEs will be listed as well as AEs among ADA positive participants.

4.2.10.2 Analysis of vital signs

Observed values and change from baseline in vital signs will be summarised by study intervention group and visit. Key participant information will be produced for vital sign parameters treatment-emergent changes outside predefined criteria (Table 23). All vital signs will be listed.

4.2.10.3 Analysis of laboratory measurements

Laboratory evaluations (continuous haematology, clinical chemistry, urinalysis and coagulation results as per Table 22) will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit. Categorical urinalysis results will be summarised in shift tables comparing maximum value during treatment to baseline value. Shifts from baseline to maximum value during treatment in haematology, clinical chemistry, urinalysis and coagulation results will be presented using low, normal and high categories. Laboratory measurements will also be summarised based on the number and percentage of participants above or below a pre-specified threshold for each test, and a listing on key participant information supporting the summary will be provided.

Continuous haematology, clinical chemistry, urinalysis and coagulation results baseline versus maximum observation on treatment will be presented in figures using shift plots.

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 25 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 • ≥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 subjects 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.

All laboratory results will be listed.

4.2.10.4 Analysis of ECG

Observed values and change from baseline in ECG variables will be summarised by visit using descriptive statistics. Key participant information will be produced for ECG parameter values outside predefined criteria (Table 24).

A shift table of categorical ECG interpretation (from best to worst: normal, abnormal - not clinically significant, abnormal - clinically significant) at baseline versus maximum (worst) observation on treatment will be provided. Abnormalities in ECG will be listed.

In addition, the number and percentage of participants with QTcF (derived as described in Section 3.8.4) changes from baseline will be presented by QTcF values >450 ms, >480 ms, >500 ms and QTcF increase from baseline >30 ms, >60 ms, >90 ms, and combination of both.

4.2.10.5 Analysis of echocardiogram

Observed values and change from baseline in LVEF will be summarised by visit using descriptive summary statistics. Echocardiogram data and abnormalities in echocardiogram will be listed.

4.2.10.6 Other safety tests

NT-proBNP results will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit. The summary based on the number and percentage of participants above or below a pre-specified threshold will be produced. NT-proBNP results will be also summarised in shift table comparing maximum value during treatment to baseline value. NT-proBNP results will be listed.

Number and proportion of participants with a negative or positive SARS-Cov-2 serology result at the end of study, who were seronegative at baseline, will be summarised. Number and proportion of participants who received a COVID-19 vaccine during the study will be included in the summary. All SARS-Cov-2 tests results (both PCR and serology) by visit will be listed for As-treated population.

5 INTERIM ANALYSES

The study team may decide to conduct an administrative un-blinded analysis of the study, prior to the Primary Analysis, with the intent to trigger internal (AstraZeneca) investment decisions. The purpose of this interim analysis would be to inform decisions on future development options for MEDI3506 or other programs. No termination of this study, or adjustments to the study design are planned. Regardless of any interim analysis results, this study will be continued and completed. As a result, no alpha will be spent at the interim analysis. Details of any interim analyses, if conducted, will be included in the Interim Analysis Plan, prepared by AstraZeneca.

6 CHANGES OF ANALYSIS FROM PROTOCOL

This SAP is based on study protocol D9180C00002 Amendment Number 5.0 dated 16 February 2022. Any further amendment of the study protocol which can have an impact on the SAP will lead to an amendment of this document. Changes of analysis from D9180C00002 Amendment Number 5.0 dated 16 February 2022 are listed here below:

Section 1.1 Synopsis

In this section is stated that “Safety endpoints including AEs, SAEs, AESIs, laboratory parameters, vital signs, ECGs, and physical examinations will be summarised using descriptive statistics.” As per this SAP we will not summarise physical examination results using descriptive statistics, as CRF 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.

Section 3 Objectives and Endpoints

There is currently no study objective/endpoint associated with CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Section 8.1.5 COPDCompEx

Additionally, night time awakenings will be removed from the list of symptoms that are considered for diary events as part of the COPDCompEx derivation in this SAP.

CCI [redacted]

Section 9.4.2.1 Primary Endpoints

In this section it is stated that the MMRM will include "The model will include fixed effects for baseline, eosinophil strata, background medication strata, visit, study intervention and the baseline by visit and study intervention by visit interactions." In this SAP it is mentioned that the MMRM will additionally include geographic region and number of exacerbations during the previous 12 months as fixed effects. The same variables will be added as fixed effects to ANCOVA, Cox proportional hazards and negative binomial models.

Sections 1.1 Synopsis, 9.4.2.1 Primary Endpoints, 9.4.2.2 Secondary Endpoints, 9.4.4.1 Patient Reported Outcomes and 9.4.4.3 Pharmacodynamic Outcomes

In all sections, the eosinophil strata is used within each model, in the SAP, it has been replaced by the log of eosinophil value at baseline.

7 REFERENCES

D9180C00002 Clinical Study Protocol – Amendment Number 4.0, 23Jul2021.

CCI [redacted]

CCI [redacted]

Smith et al 2006

Smith J, Owen E, Earis J and Woodcock A. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest 2006;130(2):379-85.

Jones et al 1991

Jones PW, Quirk FH and Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991;85 Suppl B:25-31.

Jones and Forde 2009

Jones PW and Forde Y. St George's respiratory questionnaire manual. 2009. Version 2.3. Available from URL: http://www.healthstatus.sgul.ac.uk/SGRQ_download/SGRQ%20Manual%20June%202009.pdf.

Jones et al 2009

Jones PW, Harding G, Berry P, Wiklund I, Chen WH and Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J. 2009;34(3):648-54.

8 APPENDIX

Appendix A Table of contents

Table 26 Used versions of reference documents for standard mock shells and SAP

Reference document for standard mock shells and SAP	Version	Date created
AstraZeneca Authoring Style Guide	2.0	May, 2020
AZ Corporate CSRHLD Tables Templates	3.3	July, 2020
AZ Corporate CSRHLD Figures Templates	3.2	July, 2020
AZ Corporate CSRHLD Listings Templates	1.2	July, 2020
AZ Respiratory CSRHLD Table and Figure Templates	1.0	May 14, 2019
ADA Stats Guidance	1.0	July 5, 2016
AZ Corporate CSRHLD ADA Standards	3.0	April 29, 2019
AZ Corporate CSRHLD Reporting Standards	3.2	January 31, 2020
AZ Corporate Pandemic CSRHLD Table and Listing Templates	1.0	July, 2020
AZ Oncology TA TFL Templates	3.0	April 9, 2020

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.1.1	Subject disposition (All subjects)	AZ Corporate CSRHLD Table Template COVID-summary1 (based on AZ Corporate CSR/HLD Table Template SP1)	Include Total column. Percentage for all categories are based on the number of subjects randomized Present rows relating to: • Subjects enrolled [a] • Subjects run-in • Subjects who were not run-in <<INSERT REASONS>> from CRF in sentence case • Subjects randomized • Subjects who were not randomized <<INSERT REASONS>> from CRF in sentence case • Subjects who received treatment • Subjects who did not receive treatment <<INSERT REASONS>> from CRF in sentence case • Subjects who completed treatment • Subjects who discontinued treatment <<INSERT REASONS>> from CRF in sentence case: Adverse event; Death; Lost to follow up; Non-compliance with study drug; Physician decision; Pregnancy; Protocol deviation; Site terminated by sponsor; Study terminated by sponsor; Withdrawal by subject; Other; add "Due to COVID-19 pandemic" • Subjects who completed study • Subjects withdrawn from study <<INSERT REASONS>> from CRF in sentence case: Adverse event; Death; Lost to follow up; Non-compliance with study drug; Physician decision; Pregnancy; Protocol deviation; Screen failure; Site terminated by sponsor; Study terminated by sponsor; Withdrawal by subject; Other; add "Due to COVID-19 pandemic" Include the needed footnotes for explaining terms used in the table	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.1.2	Subject disposition (ITT population)	AZ Corporate CSRHLD Table Template COVID-summary1 (based on AZ Corporate CSR/HLD Table Template SP1)	Include Total column. Categorise subjects into dose groups based on planned treatment. Percentage for all categories should be based on the number of subjects randomized Present rows relating to: • Subjects who received treatment • Subjects who completed treatment • Subjects who discontinued treatment <<INSERT REASONS>> e.g. the following: Adverse event, Death, Lost to follow up, Non-compliance with study drug, Physician decision, Pregnancy, Protocol deviation, Site terminated by sponsor, Study terminated by sponsor, Withdrawal by subjects, Due to COVID-19 pandemic, Other • Subjects who completed study • Subjects withdrawn from study <<INSERT REASONS>> from CRF in sentence case: Adverse event; Death; Lost to follow up; Non-compliance with study drug; Physician decision; Pregnancy; Protocol deviation; Screen failure; Site terminated by sponsor; Study terminated by sponsor; Withdrawal by subject; Other; add “Due to COVID-19 pandemic” Include the needed footnotes for explaining terms used in the table	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.1.3	Subject's participation in sub-study (ITT population)	AZ Corporate CSR/HLD Table Template E15	Include Total column. Percentage for all categories are based on the number of subjects in ITT population. Present rows relating to: CCI [redacted] Adverse Event Death Withdrawal by subject Due to COVID-19 pandemic Other Missing Include the needed footnotes for explaining terms used in the table	X	X	X
Table 14.1.2	Important protocol deviations (ITT population)	AZ Corporate CSRHLD Table Template COVID-summary2 (based on AZ Corporate CSR/HLD Table Template SP2)	Include Total column. Revise column heading from "Number (%) of Subjects" to "Number (%) of subjects". Refer to ECD Important Protocol Deviation guideline regarding categories for important protocol deviations, i.e. PDP. Update footnote "[a]" if the table may include important protocol deviations that occurred after end of study treatment: [a] Important protocol deviations before the start of treatment and during treatment (follow-up included). Percentage for all categories should be based on the number of subjects on each arm, i.e. N=xxx	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.3	Analysis sets (All subjects)	AZ Corporate CSR/HLD Table Template SP3	Each summary of an analysis set will account for all subjects assigned to treatment. Reasons for exclusion from safety analysis set will include "Did not receive treatment". At the end of each row label "Subjects excluded from <<…>> analysis set", include "[a]", and include footnote [a] if there is potentially more than 1 reason to exclude a subject from an analysis set. The table contains the following: • Subjects randomized • Subjects included in ITT population • Subjects excluded from ITT population[a] Did not receive treatment • Subjects included in As-treated population • Subjects excluded from As-treated population[a] Did not receive treatment • Subjects included in PK population • Subjects excluded from PK population[a] Subject did not receive any dose of MEDI3506 Missing PK measurements Non-quantifiable post-dose samples Update footnotes to include analysis set definitions to reflect SAP and protocol.	**X**	**X**	**X**
Table 14.1.4	Demographic characteristics (ITT population)	AZ Corporate CSR/HLD Table Template SP4	Include Total column. Include summaries of ethnic group. Age group categories of ≥18 - <50, ≥50 - <65, ≥65 will be modified to project-specific categories (">=40-<65" and ">=65-75"). Include age group categories for ≥18 - <65 and ≥65 for EudraCT reporting purposes.	**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.5	Subject characteristics (ITT population)	AZ Corporate CSR/HLD Table Template SP8 (with characteristics and categories specified)	Include Total column. Include height, weight and body mass index (BMI) at baseline. Weight group and BMI group are optional. Use project specific ranges for BMI group: <19, ≥19 to <25, ≥25 to <30, ≥30.	**X**		**X**
Table 14.1.6	Subject recruitment by region and country (ITT population).	AZ Corporate CSR/HLD Table Template ASP6 (with examples for stratification factors)	Include Total column. Categories, i.e. countries based on IWRS or CRF. Proposed region/countries: • North America: Canada United States • Eastern Europe: Hungary Poland Czech Republic • Western Europe: Spain Netherlands United Kingdom Germany Denmark • Rest of the world: Israel South Africa Australia New Zealand	**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.7	COPD treatments at randomization (ITT population)	AZ Respiratory CSR/HLD Table Template SP_T7	Include Total column. Non-indented row labels defined per the CSP Sn 6.5.1: • ICS + LABA, n (%) • LABA + LAMA, n (%) • ICS + LABA + LAMA, n (%) (Rows are mutually exclusive) Insert footnote(s) to define abbreviations, ICS, LABA, LAMA. Insert footnote(s) to define previous treatment/timeperiod for which treatments are collected Title should include either "previous" or "at timepoint", never both.	**X**	**X**	**X**
Table 14.1.8	Medical history (ITT population)	AZ Corporate CSR/HLD Table Template SP7(i)	Include Total column. To include any past or current medical history data (MH page from CRF). Add a footnote: Number (%) of subjects are sorted alphabetically by SOC and PT. A subject can have one or more PTs reported under a given SOC. Add a footnote to define the dictionary used within the table.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.9	COPD characteristics at study entry (ITT population)	AZ Respiratory CSR/HLD Table Template SP_T14 (Customization of AZ Corporate table template SP4, as both continuous and categorical variables are presented)	Include Total column. << Time unit>> can be "months" or "days" or "years" • Time since COPD diagnosis (years) • Time since COPD symptoms started (years) • Time since last exacerbation (months) • Total number of exacerbations within previous 12 months prior to screening (0, 1, 2, >2.) • Total number of exacerbations resulted in antibiotic treatment within previous 12 months prior to screening (0, 1, 2, >2.) • Total number of exacerbations resulted in oral steroid treatment within previous 12 months prior to screening (0, 1, 2, >2.) • Total number of exacerbations resulted in hospitalization within previous 12 months prior to screening (0, 1, 2, >2.) • Diagnosis of chronic airway obstruction (n [%]) • Diagnosis of emphysema (n [%]) • Diagnosis of obstructive chronic bronchitis (n [%]) • Chronic symptoms (n [%]) • Respiratory failure (n [%]) • Previous diagnosis of asthma (n [%]) • Diagnosis of rhinitis (n [%]) • CAT (COPD Assessment test) score.	**X**		**X**
Table 14.1.10	Diary data at baseline	AZ Respiratory CSR/HLD Table Template SP_T13		**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.11	Disposition per visit (ITT population)	AZ Respiratory CSR/HLD Table Template SP_T16	Timepoints are Week 12 to Week 36 Categories are: • Remaining on treatment (only up to and including Week 28) • Discontinued IP but still in study • Withdrawn from the study	X	X	X
Table 14.1.12	Stratification factors recorded at randomization by IWRS (ITT population)	AZ Corporate CSR/HLD Table Template ASP6	Include Total column. Present stratifications that the randomization was based on: • Baseline Blood Eosinophils CCI [redacted] • Background Medication (includes ICS; does not include ICS)	X		X
Table 14.1.13	Disallowed prior and concomitant medications during study (ITT population)	AZ Corporate CSR/HLD Table Template SP9	Include Total column. Update the version of WHODrug dictionary used for the table. Sort order: Most frequent ATC followed by generic term	X	X	X
Table 14.1.14	All allowed prior medications during study (ITT population)	AZ Corporate CSR/HLD Table Template SP10	Include Total column. Update the version of WHODrug dictionary used for the table. Define prior medications as per SAP	X	X	X
Table 14.1.15	All allowed concomitant medications during study (ITT population)	AZ Corporate CSR/HLD Table Template SP10	Include Total column. Update the version of WHODrug dictionary used for the table. Define concomitant medications as per SAP	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.1.16	Substance use, categorised (ITT population)	AZ Corporate CSR/HLD Table Template ASP2	Include Total column. Present substance usage occurrence (Never, Current, Former) and number of pack-years for: • Any substance (cigarettes, cigars, pipes) • Cigarettes • Cigars • Pipe Present substance usage occurrence (Never, Current, Former) only for: • Smokeless tobacco • Non-tobacco Nicotine products • Alcoholic beverages Include pack-year definition footnote (“Pack-years are calculated as average number of cigarettes per day × number of years / 20”).	**X**		**X**
Table 14.1.17	CCI [redacted]	AZ Respiratory CSR/HLD Table Template Q_T6 (Customization of AZ Corporate Table Template S33)	CCI [redacted]	**X**		**X**
Table 14.1.18	Summary of COVID-19 study disruptions (ITT population)	AZ Corporate CSRHLD Table Template COVID-summary3	Do not include "Subjects randomized prior to the start of COVID-19 pandemic" to "Subjects randomized post start of COVID-19 pandemic" rows	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Efficacy TOC						
Table 14.2.1.1	Lung function parameters measured in the clinic by visit, summary statistics (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate table template E7)	CCI	X	X	X
Table 14.2.1.2	Lung function parameters measured at home by 4-weekly period, summary statistics (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate table template E7)	CCI	X	X	X
Table 14.2.1.3.1	Change from baseline to Week 12 in pre-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)		X		X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.3.2	Change from baseline to Week 12 in pre-BD FEV1 (as measured in the clinic), excluding data after subjects discontinued IP, treatment comparisons, MMRM - supportive analysis (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Supportive analysis - excluding FEV1 data from after subjects have discontinued study treatment.	X		X
Table 14.2.1.3.3	Change from baseline to Week 12 in pre-BD FEV1 (as measured in the clinic) treatment comparisons by subgroups, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	FEV1 change from BL at Week 12 comparisons by subgroups.	X		X
Table 14.2.1.3.4	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.3.5	Change from baseline through Week 28 in post-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Presentation for difference in mean change from baseline in post-BD FEV1 at Weeks 12, 28 (MEDI3506–placebo). The model will include fixed effects for baseline, log-transformed eosinophil value, background medication strata, geographical region, number of exacerbations during the previous 12 months (1 vs 2 or more), visit, study intervention and the baseline by visit and study intervention by visit interactions.	X	X	X
Table 14.2.1.3.6	Change from baseline through Week 28 in post-BD FVC (as measured in the clinic) treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Presentation for difference in mean change from baseline in post-BD FVC at Weeks 12, 28 (MEDI3506–placebo). The model will include fixed effects for baseline, log-transformed eosinophil value, background medication strata, geographical region, number of exacerbations during the previous 12 months (1 vs 2 or more), visit, study intervention and the baseline by visit and study intervention by visit interactions.	X	X	X
Table 14.2.1.3.7	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.3.8	Change from baseline to Week 12 in pre-BD FEV1 (as measured in the clinic), including eosinophil strata, treatment comparisons, MMRM - sensitivity analysis 1 (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Sensitivity analysis – adding eosinophil strata instead of log-transformed eosinophil value.	**X**		**X**
Table 14.2.1.3.9	Change from baseline to Week 12 in pre-BD FEV1 (as measured in the clinic), excluding eosinophil data, treatment comparisons, MMRM - sensitivity analysis 2 (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Sensitivity analysis – excluding eosinophil value.	**X**		**X**
Table 14.2.1.3.10	Change from baseline to Week 12 in pre-BD FEV1 (as measured in the clinic), excluding implausible data, treatment comparisons, MMRM - sensitivity analysis 3 (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Sensitivity analysis – excluding implausible data.	**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.3.11	Change from baseline in pre-BD FEV1 (L) through Week 28 (as measured in the clinic) treatment comparisons by extent of emphysema, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Comparison by extent of emphysema subgroup.	**X**	X	**X**
Table 14.2.1.3.12	Change from baseline in pre-BD FEV1 (L) through Week 28 (as measured in the clinic) treatment comparisons by extent of emphysema, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Comparison by extent of emphysema subgroup.	**X**	X	**X**
Table 14.2.1.3.13	Change from baseline in pre-BD FVC (L) through Week 28 (as measured in the clinic) treatment comparisons by extent of emphysema, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Comparison by extent of emphysema subgroup.	**X**	X	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.3.14	Change from baseline in post-BD FVC (L) through Week 28 (as measured in the clinic) treatment comparisons by extent of emphysema, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Comparison by extent of emphysema subgroup.	X	X	X
Table 14.2.1.4	CCI	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI	X	X	X
Table 14.2.1.5	CCI	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.6	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X
Table 14.2.1.7.1	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	CCI [redacted]	X	X	X
Table 14.2.1.7.2	Change from baseline through Week 12 in E-RS:COPD total and domain scores treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	"Page-by" presentation for difference in mean change from baseline in: • E-RS: COPD (total and domain – breathlessness, cough and sputum, chest symptoms – scores) over the previous 4 weeks.	X		X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.7.3	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X
Table 14.2.1.8.1	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	CCI [redacted]	X	X	X
Table 14.2.1.8.2	Change from baseline through Week 12 in mean BCSS total and domain scores treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Mean BCSS total score (sum of domain scores) over the previous 4 weeks.	X		X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.8.3	CCI	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI	X	X	X
Table 14.2.1.8.4	CCI	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI	X	X	X
Table 14.2.1.9.1	CCI	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.9.2	Change from baseline through Week 12 in cough VAS average score treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	Cough VAS average score over the previous 4 weeks.	X		X
Table 14.2.1.9.3	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X
Table 14.2.1.10	SGRQ total and domain score by visit, summary statistics (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	CCI [redacted]	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.11.1	Change from baseline through Week 12 in SGRQ total and domain score treatment comparisons, MMRM (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)		X		X
Table 14.2.1.11.2	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X
Table 14.2.1.12.1	Proportion of subjects with a decrease in SGRQ total score of >= 4 points from baseline to Week 12 treatment comparisons chi-squared test (ITT population)	AZ Respiratory CSR/HLD Table Template Q_T5 (Customization of AZ Corporate Table Template E9)	Rename column Number (%) of <<type of event>>: <<Type of event>> is "decrease in total score of >=4 points from baseline to Week 12".	X		X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.12.2	CCI [redacted]	AZ Respiratory CSR/HLD Table Template Q_T5 (Customization of AZ Corporate Table Template E9)		X	**X**	**X**
Table 14.2.1.13	Airwave Oscillometry parameters by visit, summary statistics (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	"Page-by" presentation for analysed variable and change from baseline in: • R5-R20 • R5 • R20 • AX CCI [redacted] By visit (Baseline, Week 12, CCI [redacted])	**X**	**X**	**X**
Table 14.2.1.14.1	Change from baseline to Week 12 in Airwave Oscillometry parameters treatment comparisons, ANCOVA (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	"Page-by" presentation for difference in mean change from baseline in: • R5-R20 • R5 • R20 • AX CCI [redacted] At Week 12 (MEDI3506–placebo).	**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.14.2	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	**X**	**X**
Table 14.2.1.15	Objective cough measures by visit, summary statistics (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T1b (Customization of AZ Corporate table template E10)	"Page-by" presentation for analysed variable and relative change from baseline in: • Daily (ie, 24 hour) cough frequency • Night time cough frequency • Awake time cough frequency By visit (Baseline, Week 12).	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.1.16	Relative change from baseline to Week 12 in objective cough measures treatment comparisons, ANCOVA (ITT population)	AZ Respiratory CSR/HLD Table Template EF_T2b (Customization of AZ Corporate table template E7)	"Page-by" presentation for difference in mean change from baseline in: • Daily (ie, 24 hour) cough frequency • Night time cough frequency • Awake time cough frequency At Week 12 (MEDI3506 vs. placebo). Results are based on ANCOVA on log-transformed variable (calculated as visit value in log minus baseline value in log), with log(baseline value) as a covariate and study intervention, log-transformed eosinophil value, background medication strata, geographical region and number of exacerbations during the previous 12 months (1 vs 2 or more) as factors. Back-transformed results to be reported.	**X**		**X**
Figure 14.2.1.1	Change in pre-BD FEV1 measured in the clinic at Week 12, MMRM - forest plot by subgroups (ITT population)	AZ Corporate CSR/HLD Figure Template E5		**X**		**X**
Figure 14.2.1.2.1	Change from baseline to Week 12 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**
Figure 14.2.1.2.2	Change from baseline to Week 12 in pre-BD FEV1 measured in the clinic, excluding data after subjects discontinued IP, LSMeans (80% CI) - supportive analysis (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.2.1.2.3	Change from baseline to Week 12 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI) by subgroups (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**
Figure 14.2.1.2.4	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.3	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.4	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.5	Change from baseline through Week 28 in post-BD FEV1 measured in the clinic, LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.2.1.6	Change from baseline through Week 28 in post-BD FVC measured in the clinic, LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.7	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.8	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.9.1	Change from baseline through Week 12 in ER-S:COPD (total and domain scores), LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**
Figure 14.2.1.9.2	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.2.1.10.1	Change from baseline through Week 12 in BCSS (total and domain scores), LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**
Figure 14.2.1.10.2	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.11.1	Change from baseline through Week 12 in cough VAS, LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**
Figure 14.2.1.11.2	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		**X**	**X**	**X**
Figure 14.2.1.12.1	Change from baseline to Week 12 in SGRQ total and domain score, LSMeans (80% CI) (ITT population)	AZ Corporate CSR/HLD Figure Template E4		**X**		**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.2.1.12.2	CCI	AZ Corporate CSR/HLD Figure Template E4		X	X	X
Figure 14.2.1.13	CCI	AZ Corporate CSR/HLD Figure Template E4		X	X	X
Table 14.2.2.1.1	CCI	AZ Respiratory CSR/HLD Table Template Q_T4 (Customization of AZ Corporate Table Template E6, has been transposed and has been modified to exclude the between-treatment comparisons)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.1.2	CCI	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	CCI	X	X	X
Table 14.2.2.1.3	CCI	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI	X	X	X
Figure 14.2.2.1	CCI	AZ Corporate CSR/HLD Figure Template E4		X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.1	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T6 (Possibly a customization of AZ Corporate Table Template E15)	CCI [redacted]	**X**	**X**	**X**
Table 14.2.2.2.2	Medication used due to worsening in COPD symptoms (ITT population)	AZ Respiratory CSR/HLD Table Template EX_T5 (Customization of AZ Corporate Table Template E2)	Medication categories as per CRF: • Loop Diuretics • Antibiotics • Systemic Corticosteroids (injected and/or oral) Repeat descriptive statistics for: • Total days of medication use per subject • Total dose of medication use per subject	**X**	**X**	**X**
Table 14.2.2.2.3	COPDCompEx events, summary statistics (ITT population)	AZ Respiratory CSR/HLD Table Template EX_T1b (Customization of AZ Corporate Table Template E10 and E13)	Use rows for COPDCompEx defined exacerbations: • All exacerbations <Subjects with at least one exacerbation n (%), Total number of subject-treatment years[a], Number of subjects with exacerbations/subject-treatment year> Add rows for Diary events: • Overall symptom rating increase from baseline CCI [redacted] • PEF (Peak expiratory flow) decrease from baseline	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.4	Time to first COPDCompEx event (days) - Cox-regression analysis (ITT population)	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	Time to first COPDCompEx event will be analysed using a Cox proportional hazard model, with study intervention, log-transformed eosinophil value, background medication strata, geographical region and number of exacerbations during the previous 12 months (1 vs 2 or more) fitted as covariates. Analysis of time to event CCI [redacted] will include available data from the complete variable intervention period (period from baseline to Week 28) for all participants. Change column header from “Exacerbation” to “CompEx event”, rows similar to EX_T1b.	X	X	X
Table 14.2.2.2.5	COPDCompEx events over the period from baseline to Week 28, negative binomial regression (ITT population)	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	Summary includes number of events, total follow-up time, annual CompEx event rate, rate ratio comparison (MEDI3506 vs. placebo).	X	X	X
Table 14.2.2.2.6	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T1b (Customization of AZ Corporate Table Template E10 and E13)	CCI [redacted]	CCI [redacted]		

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.7	CCI	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)		X	X	X
Table 14.2.2.2.8	CCI	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)		X		X
Table 14.2.2.2.9	CCI	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.10	CCI	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI	X		X
Table 14.2.2.2.11	CCI	AZ Corporate CSR/HLD Table Template E5	CCI	X		X
Table 14.2.2.2.12	CCI	AZ Corporate CSR/HLD Table Template E5	CCI		X	X
Table 14.2.2.2.13	CCI	AZ Respiratory CSR/HLD Table Template EX_T1b (Customization of AZ Corporate Table Template E10 and E13)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.14	CCI	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	CCI	X	X	X
Table 14.2.2.2.15	CCI	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI	X	X	X
Table 14.2.2.2.16	CCI	AZ Respiratory CSR/HLD Table Template EX_T1b (Customization of AZ Corporate Table Template E10 and E13)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.17	CCI	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	CCI	X	X	X
Table 14.2.2.2.18	CCI	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	CCI	X		X
Table 14.2.2.2.19	CCI	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.20	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI [redacted]	**X**		**X**
Table 14.2.2.2.21	Time to first COPDCompEx event (days) - Cox-regression analysis by extent of emphysema (ITT population)	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	Comparison by extent of emphysema subgroup.	**X**		**X**
Table 14.2.2.2.22	COPDCompEx events on treatment, summary statistics by eosinophils	AZ Respiratory CSR/HLD Table Template EX_T1b (Customization of AZ Corporate Table Template E10 and E13)	CCI [redacted]	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.23	Time to first COPDCompEx event (days) - Cox-regression analysis by eosinophils (ITT population)	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	CCI [redacted]	X	X	X
Table 14.2.2.2.24	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI [redacted]	X	X	X
Table 14.2.2.2.25	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T1b (Customization of AZ Corporate Table Template E10 and E13)	CCI [redacted]	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.26	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	CCI [redacted]	X	X	X
Table 14.2.2.2.27	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T4b (Customization of AZ Corporate Table Template E5)	CCI [redacted]	X		X
Table 14.2.2.2.28	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI [redacted].	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.2.29	CCI	AZ Respiratory CSR/HLD Table Template EX_T2 (Customization of AZ Corporate Table Template E14)	CCI	X		X
Figure 14.2.2.2.1	Time to first COPDCompEx event (days), Kaplan-Meier plot (ITT population)	AZ Corporate CSR/HLD Figure Template E1		X	X	X
Figure 14.2.2.2.2	CCI	AZ Corporate CSR/HLD Figure Template E1		X	X	X
Table 14.2.2.3.1	CCI	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate CSR/HLD Table Template E10)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.3.2	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X	X	X
Figure 14.2.2.3.1	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		X	X	X
Table 14.2.2.4.1	Summary of serum concentrations (ug/L) of MEDI3506 (PK population)	AZ Corporate CSR/HLD Table Template PK3(i)	Include summary statistics for serum concentrations of MEDI3506.	X	X	X
Table 14.2.2.4.2	Summary of serum concentrations (ug/L) of MEDI3506 over time by Anti-Drug Antibody category (PK population)	AZ Corporate CSR/HLD ADA Table Template PKADA1	MEDI3506 concentrations can be summarised by visit and ADA status (positive/negative) using descriptive statistics. Individual concentration time profiles per subject can be added.	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.2.2.4.1	Geometric mean (gSD) serum concentrations (ug/L) of study intervention versus time (Linear scale) (PK population)	AZ Corporate CSR/HLD Figure Template PK2	X-Axis is timepoint: Baseline (Week 0), Weeks 2, 4, 12, 20, 24, 28, 32, 36	X	X	X
Figure 14.2.2.4.2	Individual serum concentrations (ug/L) of study intervention versus time (Linear scale) (PK population)	AZ Corporate CSR/HLD Figure Template PK3	Y-axis is Concentration (ug/L) X-axis is timepoint: Baseline (Week 0), Weeks 2, 4, 12, 20, 24, 28, 32, 36	X	X	X
Figure 14.2.2.4.3	Individual serum concentrations (ug/L) time profile of MEDI3506 by Anti-Drug Antibody category – spaghetti plot (PK population)	AZ Corporate CSR/HLD ADA Figure Template PKADA1		X	X	X
Table 14.2.2.5.1	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T1b (Customization of AZ Corporate table template E10)	CCI [redacted]	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.5.2	CCI	AZ Respiratory CSR/HLD Table Template EF_T2b (Customization of AZ Corporate table template E7)	CCI		X	X
Figure 14.2.2.5.1	CCI	AZ Corporate CSR/HLD Figure Template E4			X	X
Table 14.2.2.5.3	CCI	AZ Respiratory CSR/HLD Table Template EF_T1b (Customization of AZ Corporate table template E10)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.5.4	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]	X		X
Table 14.2.2.5.5	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2b (Customization of AZ Corporate table template E7)	CCI [redacted]	X		X
Table 14.2.2.5.6	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI [redacted]		X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.2.5.7	CCI [redacted]	AZ Respiratory CSR/HLD Table Template EF_T2b (Customization of AZ Corporate table template E7)	CCI [redacted]		X	X
Figure 14.2.2.5.2	CCI [redacted]	AZ Corporate CSR/HLD Figure Template E4		X	X	X
Immunogenicity TOC						
Table 14.2.3.1	Summary of Anti-Drug Antibody responses during the study (As-treated population)	SPADA1	By ADA categories (to confirm): • ADA positive at baseline and/or post-baseline (ADA prevalence) • TE-ADA positive (ADA incidence) • Treatment-induced ADA positive • Treatment-boosted ADA positive • Non-TE-ADA positive • Both baseline and post-baseline positive • ADA negative • Only baseline positive • ADA persistently positive • ADA transiently positive • TE-ADA positive with maximum titre > median of maximum titres	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.3.2	Anti-Drug Antibody results and titre summary by timepoint (As-treated population)	SPADA3	• To present descriptive statistics of ADA titre by visit (SV3, SV5, SV6, SV8, SV10, SV11, SV12, SV13, SV14, E/D)	**X**	**X**	**X**
Table 14.2.3.3	Pre-BD FEV1 (as measured in the clinic) at Week 12 by Anti-Drug Antibody category, summary statistics	EADA1		**X**	**X**	**X**
Table 14.2.3.4	Pre-BD FEV1 (as measured in the clinic) at Week 28 by Anti-Drug Antibody category, summary statistics	EADA1		**X**	**X**	**X**
Table 14.2.3.5	CCI [redacted]	EADA1		**X**	**X**	**X**
Table 14.2.3.6	Adverse events during the treatment and follow-up periods in any category by Anti-Drug Antibody category	SADA1		**X**	**X**	**X**
Table 14.2.3.7	Number of subjects with adverse events by system organ class and preferred term by Anti-Drug Antibody category	NEW3		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.4.1	CCI	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate table template E10)	CCI		X	X
Table 14.2.4.2	CCI	AZ Respiratory CSR/HLD Table Template EF_T2a (Customization of AZ Corporate table template E7)	CCI		X	X
Table 14.2.5.1	CCI	AZ Respiratory CSR/HLD Table Template EF_T1a (Customization of AZ Corporate table template E10)	CCI	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.2.5.2	CCI	AZ Respiratory CSR/HLD Table Template EF_T2b (Customization of AZ Corporate table template E7)	CCI	X	X	X
Table 14.2.5.3	CCI	AZ Corporate CSR/HLD Table Template S27		X	X	X
Figure 14.2.5.1	CCI	AZ Corporate CSR/HLD Figure Template E4		X	X	X
Exploratory Biomarker TOC						
CCI						

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
CCI						

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
CCI [redacted]						
Safety TOC						
Table 14.3.1.1	Duration of exposure (As-treated population)	AZ Corporate CSR/HLD Table Template S1	Do not include Total column. Present summary statistics for duration of exposure and cumulative exposure over time. Cumulative exposure is optional. In inclusion case, include it in the title as well. Duration of exposure definition to be added.	**X**	**X**	**X**
Table 14.3.1.2	Treatment interruptions for Investigational Product (As-treated population)	AZ Corporate CSR/HLD Table Template AS13		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.2.1	Number of subjects with adverse events in any category (As-treated population)	AZ Corporate CSR/HLD Table Template S5	Specify the period/periods which AE will be reported for, in the footnote. Include the following AE categories: • Any AE • Any AE of toxicity grade 4 or 5 • Any AE with outcome = death • Any SAE (including events with outcome = death) • Any AE leading to discontinuation of IP • Any AE leading to dose interruption • Any AE leading to withdrawal from study • Any AESI	**X**	**X**	**X**
Table 14.3.2.2	Adverse events in any category - event counts (As-treated population)	AZ Corporate CSR/HLD Table Template S6	Present the same categories of AE as in S5	**X**	**X**	**X**
Table 14.3.2.3	Number of subjects with adverse events, by system organ class (As-treated population)	AZ Corporate CSR/HLD Table Template S7	<<event rate>> will not be included.	**X**	**X**	**X**
Table 14.3.2.4	Number of subjects with adverse events by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S9(i)	Specify the period/periods which AE will be reported for, in the footnote [a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetical order for preferred term. Subjects with multiple events in the same preferred term are counted only once in that preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.2.5	Number of adverse events, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S16(i)		**X**	**X**	**X**
Table 14.3.2.6	Number of subjects with adverse events, most common (frequency of >5%), by preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S8	Specify the period/periods which AE will be reported for, in the footnote Number (%) of subjects with AEs, sorted in decreasing frequency for preferred term (sorted by MEDI3506 treatment group) The cut off used is to be clearly stated in the title and footnote. The difference between S8 and FDAAA1 is – in S8 most common are defined as % in Total group, not individual treatment groups – and in FDAAA1 it is % in any treatment group.	**X**	**X**	**X**
Table 14.3.2.7	Non-serious adverse events occurring in greater than 5% of subjects (As-treated population)	AZ Corporate CSR/HLD Table Template FDAAA1		**X**	**X**	**X**
Table 14.3.2.8	Number of subjects with adverse events, by preferred term and maximum reported toxicity grade (As-treated population)	AZ Oncology CSR/HLD Table Template TAE050 - TA specific version of AZ Corporate CSR/HLD Table Template S10	Specify the period/periods which AE will be reported for, in the footnote Each subject has only been represented with the maximum reported toxicity grade for each preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred terms. Each subject is counted only once (by their maximum reported toxicity grade) within a treatment group in this overall summary.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.2.9	Number of subjects with adverse events, by preferred term and relationship as assessed by investigator (As-treated population)	AZ Corporate CSR/HLD Table Template S11	<<event rate>> will not be included.	**X**	**X**	**X**
Table 14.3.2.10	Number of subjects with adverse events, leading to dose interruption of IP, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S_T1		**X**	**X**	**X**
Table 14.3.2.11	Number of subjects with COVID-19 related adverse events by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S9(i)		**X**	**X**	**X**
Table 14.3.3.1	Number of subjects with adverse events with outcome of death, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S13(i)	Specify the period/periods which AE will be reported for, in the footnote Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 25.1 or higher used	**X**	**X**	**X**
Table 14.3.3.2	Adverse Events with outcome of death - key subject information (As-treated population)	AZ Corporate CSR/HLD Table Template S14	Specify the period/periods which AE will be reported for, in the footnote	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.4.1.1	Number of serious adverse events, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S16(ii)	Specify the period/periods which AE will be reported for, in the footnote	**X**	**X**	**X**
Table 14.3.4.1.2	Number of subjects with serious adverse events, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S17(i)		**X**	**X**	**X**
Table 14.3.4.1.3	Number of subjects with COVID-19 related serious adverse events, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S17(i)		X	X	X
Table 14.3.4.2	Serious adverse events - key subject information (As-treated population)	AZ Corporate CSR/HLD Table Template S18		**X**	**X**	**X**
Table 14.3.5.1	Number of subjects with adverse events leading to discontinuation of investigational product, by system organ class and preferred term (As-treated population)	AZ Corporate CSR/HLD Table Template S19(i)	Specify the period/periods which AE will be reported for, in the footnote MedDRA version 25.1 or higher used	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.5.2	Adverse events leading to discontinuation of investigational product - key subject information (As-treated population)	AZ Corporate CSR/HLD Table Template S20	MedDRA version 25.1 or higher used	**X**	**X**	**X**
Table 14.3.6.1	Adverse events of special interest - list of preferred terms	AZ Corporate CSR/HLD Table Template AS9		**X**	**X**	**X**
Table 14.3.6.2	Number of subjects with adverse events of special interest, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**
Table 14.3.6.3	Number of subjects with adverse events of ISR, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**
Table 14.3.6.4	Number of subjects with adverse events of serious hypersensitivity, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.6.5	Number of subjects with adverse events of serious infection, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**
Table 14.3.6.6	Number of subjects with adverse events of progression of heart failure, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**
Table 14.3.6.7	Number of subjects with adverse events of gastrointestinal adverse reactions, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**
Table 14.3.6.8	Number of subjects with adverse events of COVID-19, by maximum reported toxicity grade (As-treated population)	AZ Corporate CSR/HLD Table Template AS8		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.7.1.1	Haematology laboratory variables over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25 (applied to Laboratory Data)	Choose timepoints relevant to the study: SV1, SV3, SV5, SV6, SV8, SV10, SV12, SV13, SV14, E/D Labels as per SAP Analysis Visit Windows. Report summary statistics Include Q1 and Q3 Include in the summary all haematology and clinical chemistry parameters listed in the protocol.	**X**	**X**	**X**
Table 14.3.7.1.2	Clinical chemistry laboratory variables over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25 (applied to Laboratory Data)	Choose timepoints relevant to the study: SV1, SV3, SV5, SV6, SV8, SV10, SV12, SV13, SV14, E/D Labels as per SAP Analysis Visit Windows. Report summary statistics Include Q1 and Q3 Include in the summary all clinical chemistry parameters listed in the protocol.	**X**	**X**	**X**
Table 14.3.7.1.3	Urinalysis laboratory variables over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25 (applied to Laboratory Data)	Choose timepoints relevant to the study: SV1, SV3, SV5, SV6, SV8, SV10, SV12, SV13, SV14, E/D Labels as per SAP Analysis Visit Windows. Report summary statistics Include Q1 and Q3 Include in the summary all clinical chemistry parameters listed in the protocol.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.7.1.4	Coagulation laboratory variables over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25 (applied to Laboratory Data)	Choose timepoints relevant to the study: SV1, SV3, SV5, SV6, SV8, SV10, SV12, SV13, SV14, E/D Labels as per SAP Analysis Visit Windows. Report summary statistics Include Q1 and Q3 Include in the summary all clinical chemistry parameters listed in the protocol.	**X**	**X**	**X**
Table 14.3.7.2.1	Haematology laboratory variables, baseline versus maximum observation on treatment (As-treated population)	AZ Corporate CSR/HLD Table Template S27	Define baseline measurement in the footnotes	**X**	**X**	**X**
Table 14.3.7.2.2	Clinical chemistry laboratory variables, baseline versus maximum observation on treatment (As-treated population)	AZ Corporate CSR/HLD Table Template S27	Define baseline measurement in the footnotes	**X**	**X**	**X**
Table 14.3.7.2.3	Urinalysis laboratory variables, baseline versus maximum observation on treatment (As-treated population)	AZ Corporate CSR/HLD Table Template S27	Define baseline measurement in the footnotes	**X**	**X**	**X**
Table 14.3.7.2.4	Coagulation laboratory variables, baseline versus maximum observation on treatment (As-treated population)	AZ Corporate CSR/HLD Table Template S27	Define baseline measurement in the footnotes	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.7.4	Maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's Law criteria (As-treated population)	AZ Corporate CSR/HLD Table Template AS14		**X**	**X**	**X**
Table 14.3.7.5	Subjects with potential Hy's Law - individual subject data (As-treated population)	AZ Corporate CSR/HLD Table Template S32	"If there are subjects who met the criteria specified. A potential Hy's Law case is defined as any situation where a study subject has an increase in both AST or ALT ≥ 3×ULN and TBL ≥ 2×ULN, irrespective of ALP, at any point during the study. " Multiple of ULN is defined as value divided by ULN, i.e. if the ALT value was X (ULN = Y) then the multiple would be X/Y.	**X**	**X**	**X**
Table 14.3.7.6	Urinalysis, baseline versus maximum observation on treatment, shift table (As-treated population)	AZ Corporate CSR/HLD Table Template S33	Define baseline measurement in the footnotes	**X**	**X**	**X**
Figure 14.3.7.1	Haematology laboratory variables, baseline versus maximum observation on treatment – shift plot (As-treated population)	AZ Corporate CSR/HLD Figure Template S8			**X**	**X**
Figure 14.3.7.2	Clinical chemistry laboratory variables, baseline versus maximum observation on treatment – shift plot (As-treated population)	AZ Corporate CSR/HLD Figure Template S8			**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.3.7.3	Urinalysis laboratory variables, baseline versus maximum observation on treatment – shift plot (As-treated population)	AZ Corporate CSR/HLD Figure Template S8			**X**	**X**
Figure 14.3.7.4	Coagulation laboratory variables, baseline versus maximum observation on treatment – shift plot (As-treated population)	AZ Corporate CSR/HLD Figure Template S8			**X**	**X**
Figure 14.3.7.5	ALT versus total bilirubin, expressed as multiples of ULN (As-treated population)	AZ Corporate CSR/HLD Figure Template S9	This must be produced for both ALT and AST. Also, that the preferred approach for the plot is that it should be produced on the log scale, and reference lines must be included at 2xULN for total bilirubin and at 3xULN for ALT/AST. Reference lines at 3*ULN of ALT /AST and 2*ULN for total bilirubin are compulsory Multiple of ULN is defined as value divided by ULN, i.e. if the ALT value was X (ULN = Y) then the multiple would be X/Y. Additional reference lines may be added, if so, please ensure compulsory reference lines must be easily identified	**X**	**X**	**X**
Figure 14.3.7.6	AST versus total bilirubin, expressed as multiples of ULN (As-treated population)	AZ Corporate CSR/HLD Figure Template S9	This must be produced for both ALT and AST. Also, that the preferred approach for the plot is that it should be produced on the log scale, and reference lines must be included at 2xULN for total bilirubin and at 3xULN for ALT/AST. Reference lines at 3*ULN of ALT /AST and 2*ULN for total bilirubin are compulsory Multiple of ULN is defined as value divided by ULN, i.e. if the ALT value was X (ULN = Y) then the multiple would be X/Y.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Figure 14.3.7.7	Liver biochemistry test results over time – subjects with elevated ALT or AST, and elevated total bilirubin, at any time (As-treated population)	AZ Corporate CSR/HLD Figure Template S10		**X**	**X**	**X**
Table 14.3.8.1.1	Vital signs variables over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25(vital) (applied to Vital Signs data).	Use relevant timepoints for the study: SV3, SV5, SV6, SV7, SV8, SV9, SV10, SV11, SV12, SV13, SV14, E/D at timepoints Pre-Dose; Post-Dose; 0.5H Post-Dose; 1H Post-Dose; 2H Post-Dose. Labels as per SAP Analysis Visit Windows and Timepoints. Define baseline measurement in the footnotes Vital signs variables (temperature; DBP; SBP; Heart rate; Respiratory rate) should be presented in same way for Lab data. (incl. Q1 and Q3)	**X**	**X**	**X**
Table 14.3.8.1.2	Vital signs, treatment-emergent changes outside predefined criteria – key subject information (As-treated population)	AZ Corporate CSR/HLD Table Template AS3	Use relevant timepoints for the study: SV3, SV5, SV6, SV7, SV8, SV9, SV10, SV11, SV12, SV13, SV14, E/D at timepoints Pre-Dose; Post-Dose; 0.5H Post-Dose; 1H Post-Dose; 2H Post-Dose. Labels as per SAP Analysis Visit Windows and Timepoints. Define baseline measurement in the footnotes Vital signs variables (temperature; DBP; SBP; Heart rate; Respiratory rate) should be presented in same way for Lab data.			**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.8.2.1	ECG variables, over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25(ecg).	Use relevant timepoints for the study: SV1, SV3, SV8, SV12, SV14, E/D Labels as per SAP Analysis Visit Windows Report summary statistics (incl. Q1 and Q3)	**X**	**X**	**X**
Table 14.3.8.2.2	QTcF intervals, change from baseline to any postbaseline observation (As-treated population)	AZ Corporate CSR/HLD Table Template S35 (transposed)	Title and column headers should indicate which formula is being used and this should then be footnoted e.g., "QTcB calculated using Bazett's formula" or; "QTcF calculated using Fridericia's formula" or "QTc'X' calculated using <<>> formula". Define baseline measurement in the footnotes	**X**	**X**	**X**
Table 14.3.8.2.3	ECG values outside predefined criteria – key subject information (As-treated population)	AZ Corporate CSR/HLD Table Template AS4				**X**
Table 14.3.8.2.4	ECG, baseline versus maximum observation on treatment (As-treated population)	AZ Corporate CSR/HLD Table Template S41 (applied to ECG data).	Update column header from "Assessment at end of treatment" to "Maximum value during treatment"	**X**	**X**	**X**
Table 14.3.8.3.1	Left ventricular ejection fraction (%), over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25(echoc)		**X**	**X**	**X**
Table 14.3.8.3.2	NT-proBNP data over time (As-treated population)	AZ Corporate CSR/HLD Table Template S25 (applied to Laboratory Data)		**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Table 14.3.8.3.3	NT-proBNP baseline to maximum value during treatment (As-treated population)	AZ Corporate CSR/HLD Table Template S27		**X**	**X**	**X**
Table 14.3.8.3.5	Other safety tests – COVID-19 related (As-treated population)	NEW1	Number of participants seropositive for SARS-CoV-2 at end of study who were seronegative at randomization visit.	**X**	**X**	**X**
Appendix 16.1.6	Subjects receiving the various batches of investigational products (All randomized subjects)	AZ Corporate CSR/HLD Listing Template APL22				**X**
Appendix 16.1.7	Randomization scheme and codes (All randomized subjects)	AZ Corporate CSR/HLD Listing Template APL23				**X**
Appendix 16.2.1.1	Discontinued subjects (All subjects)	AZ Corporate CSR/HLD Listing Template 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 • Randomization • Study discontinued due to <<insert reason for discontinuation from EOS form in lower case, e.g. adverse event >>	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.1.2	Subjects completing the study (All subjects)	AZ Corporate CSR/HLD Listing Template APL02	Optional. Standardised disposition terms should include: • Informed consent obtained • Randomization • Study completed	**X**	**X**	**X**
Appendix 16.2.1.3	Subjects affected by the COVID-19 pandemic (ITT population)	AZ Corporate CSR/HLD Listing Template 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.	**X**	**X**	**X**
Appendix 16.2.2.1	Subjects with important protocol deviations (ITT population)	AZ Corporate CSR/HLD Listing Template APL03	Sort this listing by: Short subject identifier, Description of planned arm, Date/Time of collection.	**X**	**X**	**X**
Appendix 16.2.2.2	Subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic (ITT population)	AZ Corporate CSR/HLD Listing Template APL-COVID2	This listing is to satisfy the AZ Data Integrity document requirement Please note that important Protocol Deviations and COVID-19 related non-important PDs and issues will be part of the CSR.	**X**	**X**	**X**
Appendix 16.2.3.1	Subjects excluded from any analysis set (All subjects)	AZ Corporate CSR/HLD Listing Template APL04	Sort this listing by: Short subject identifier, Description of planned arm. Add column for Description of Actual arm.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.4.1	Demographic and baseline characteristics (ITT population)	AZ Corporate CSR/HLD Listing Template APL06	Sort this listing by: Short subject identifier, Description of planned arm. Analysis set - All subjects (including screen failures)	**X**	**X**	**X**
Appendix 16.2.4.2	Lung function data at baseline (ITT population)	AZ Corporate CSR/HLD Listing Template APL07		X		**X**
Appendix 16.2.4.3	Concomitant medication on entry and during the study (ITT population)	AZ Corporate CSR/HLD Listing Template APL08		X	**X**	**X**
Appendix 16.2.5.1	Administration of investigational product (As-treated population)	AZ Corporate CSR/HLD Listing Template 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 excluded. The listing should be adjusted according to the administration data collected and the type of study/treatment.	**X**	**X**	**X**
Appendix 16.2.6.1.1	Individual efficacy response data – exacerbations (ITT population)	AZ Corporate CSR/HLD Listing Template APL10	Sort this listing by: Short subject identifier, Description of planned arm CCI [redacted]	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.6.1.2	CompEx events (ITT population)	New 4		**X**	**X**	**X**
Appendix 16.2.6.1.3	Efficacy assessments – clinic spirometry (ITT population)	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Parameter" are: • Pre-BD FEV_1 • Pre-BD FVC • FEV_1/FVC ratio • Post-BD FEV_1 • Post-BD FVC CCI [redacted]	**X**	**X**	**X**
Appendix 16.2.6.1.4	Efficacy assessments – [redacted] (ITT population)	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Parameter" are: CCI [redacted]	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.6.1.5	Efficacy assessments - Airwave Oscillometry (ITT population)	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Page" and "Parameter" are: • R5-R20 • R5 • R20 • AX CCI [redacted]	X	X	X
Appendix 16.2.6.1.6	Efficacy assessments – cough measures (ITT population)	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Parameter" are: • Daily cough frequency • Night time cough frequency • Awake time cough frequency	X	X	X

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.6.1.7	Efficacy assessments - Electronic Patient Reported Outcome (ITT population)	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Parameter" are: • E-RS:COPD • Mean BCSS score (over the previous 4 weeks) • Cough VAS item (average over previous 4 weeks) • SGRQ domain score • SGRQ total score CCI [redacted] • CAT	**X**	**X**	**X**
Appendix 16.2.6.1.8	CCI [redacted]	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Parameter" are: CCI [redacted]	**X**	**X**	**X**
Appendix 16.2.6.1.9	CCI [redacted]	AZ Corporate CSR/HLD Listing Template APL11	"By page" listing of Primary, secondary endpoints, CCI [redacted] Drop "Site of assessment" and "Method of assessment" columns. "Parameter" are: CCI [redacted] as listed in the SAP	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.6.2.1	Drug concentration data (PK population)	AZ Corporate CSR/HLD Listing Template APL13		X	**X**	**X**
Appendix 16.2.6.3.1	Anti-Drug Antibody results (As-treated population)	SPADA1	Sort this listing by: Subject identifier within treatment group. ADA study status provided may include ADA negative, treatment-induced ADA positive, treatment-boosted ADA positive, TE-ADA negative, persistently positive, transiently positive, ADA positive at baseline only, etc.... The goal is to ensure that all applicable ADA categories are listed for each subject in the listing. If a subject is included in more than one category, they should all be listed. For example, a subject may be persistently positive and treatment-induced ADA positive.	**X**	**X**	**X**
Appendix 16.2.6.3.2	Listing of ADA positive subjects, key subject information (As-treated population)	SPADA3	Sort by treatment group and subject identifier. Include all subjects with a positive ADA result at baseline and/or post-baseline.	**X**	**X**	**X**
Appendix 16.2.7.1.1	Adverse events (As-treated population)	AZ Corporate CSR/HLD Listing Template APL14	Mention the used Med dictionary (MedDRA v25.1 or higher), in the footnotes. Sort this listing by: Short subject identifier, Treatment/Period, and Preferred term. Note that it may be more applicable to sort by Treatment start date and AE start date than Treatment/Period (ie, alphabetically), although these data are not presented in the listing.	**X**	**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.7.1.2	Adverse events among Anti-Drug Antibody positive subjects (As-treated population)	SADA1		**X**	**X**	**X**
Appendix 16.2.7.2	Adverse events for enrolled but not randomized subjects and for subjects who were not exposed to treatment	AZ Corporate CSR/HLD Listing Template APL15				**X**
Appendix 16.2.8.1.1	Individual laboratory measurement - Haematology (As-treated population)	AZ Corporate CSR/HLD Listing Template APL16	Sort this listing by: Short subject identifier, Description of actual arm, Lab test or examination name, Analysis visit, planned time point name. The study team will decide about which lab variables to include in this listing Unique values used for analysis will be flagged with asterisk (*) (i.e. repeated measurements outside visit windows will not be flagged)		**X**	**X**
Appendix 16.2.8.1.2	Individual laboratory measurement – Clinical chemistry (As-treated population)	AZ Corporate CSR/HLD Listing Template APL16	Sort this listing by: Short subject identifier, Description of actual arm, Lab test or examination name, Analysis visit, planned time point name. The study team will decide about which lab variables to include in this listing Unique values used for analysis will be flagged with asterisk (*) (i.e. repeated measurements outside visit windows will not be flagged)		**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.8.1.3	Individual laboratory measurement – Coagulation (As-treated population)	AZ Corporate CSR/HLD Listing Template APL16	Sort this listing by: Short subject identifier, Description of actual arm, Lab test or examination name, Analysis visit, planned time point name. The study team will decide about which lab variables to include in this listing Unique values used for analysis will be flagged with asterisk (*) (i.e. repeated measurements outside visit windows will not be flagged)		**X**	**X**
Appendix 16.2.8.1.4	Individual laboratory measurement - Urinalysis (As-treated population)	AZ Corporate CSR/HLD Listing Template APL16	Sort this listing by: Short subject identifier, Description of actual arm, Lab test or examination name, Analysis visit, planned time point name. The study team will decide about which lab variables to include in this listing Unique values used for analysis will be flagged with asterisk (*) (i.e. repeated measurements outside visit windows will not be flagged)		**X**	**X**
Appendix 16.2.8.2	Laboratory safety variables (As-treated population)	AZ Corporate CSR/HLD Listing Template APL17	Sort this listing by: Short subject identifier, Description of actual arm, Lab test or examination name, Analysis visit. The listing will present results from the following tests: • SARS-CoV-2 (serology and nucleic acid test)		**X**	**X**
Appendix 16.2.9.1	Individual vital signs data (As-treated population)	AZ Corporate CSR/HLD Listing Template APL18	Unique values used for analysis will be flagged with asterisk (*)		**X**	**X**

TLF number	Title	Standard mock shell reference	Additional Information	Analysis1 (Week 12)	Analysis2 (Week 28)	Final Analysis
Appendix 16.2.10.1	Electrocardiogram data (As-treated population)	AZ Corporate CSR/HLD Listing Template APL19	Unique values used for analysis will be flagged with asterisk (*)		**X**	**X**
Appendix 16.2.10.2	Abnormalities in electrocardiogram (As-treated population)	AZ Corporate CSR/HLD Listing Template APL20	Rename columns to match with CRF content: Specification of ECG finding -> Reason, abnormal overall ECG evaluation		**X**	**X**
Appendix 16.2.10.3	Echocardiogram data (As-treated population)	NEW2		**X**	**X**	**X**
Appendix 16.2.10.4	Individual NT-proBNP data (As-treated population)	AZ Corporate CSR/HLD Listing Template APL16	Similar to Laboratory data listing, rename columns: Lab test or examination name -> Test or examination name (use NT-proBNP as default) Remove Category for lab test column	**X**	**X**	**X**

Appendix B ePRO scoring

B 1 Calculation of E-RS™: COPD scores

Table 27 E-RS™: COPD scoring

Domain	Item (number)	Patient's Response / Score
Breathlessness	Breathless today (7): Were you breathless today?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 4
	Breathless with activity (8): Describe how breathless you were today:	Unaware of breathlessness = 0 Breathless during strenuous activity = 1 Breathless during light activity = 2 Breathless when washing or dressing = 3 Present when resting = 3
	Short of breath – personal care (9): Were you short of breath today when performing your usual personal care activities like washing or dressing?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 3 Too breathless to do this = 4
	Short of breath – indoor activity (10): Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 3 Too breathless to do this = 3
	Short of breath – outdoor activity (11): Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 3 Too breathless to do this = 3
Cough and Sputum	Cough frequency (2): How often did you cough today?	Not at all = 0 Rarely = 1 Occasionally = 2 Frequently = 3 Almost constantly = 4

Domain	Item (number)	Patient's Response / Score
	Mucus quantity (3): How much mucus (phlegm) did you bring up when coughing today?	None at all = 0 A little = 1 Some = 1 A great deal = 2 A very great deal = 3
	Difficulty with mucus (4): How difficult was it to bring up mucus (phlegm) today?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 4
Chest symptoms	Congestion (1): Did your chest feel congested today?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 4
	Discomfort (5): Did you have chest discomfort today?	Not at all = 0 Slight = 1 Moderate = 2 Severe = 3 Extreme = 4
	Tightness (6): Did your chest feel tight today?	Not at all = 0 Slightly = 1 Moderately = 2 Severely = 3 Extremely = 4

B 2 CCI

CCI

[redacted]

CCI

CCI

B 3 Calculation of SGRQ scores

Each questionnaire response has a unique empirically derived 'weight'. The lowest possible weight is zero and the highest is 100.

Each component of the questionnaire is scored separately in three steps:

1 The weights for all items with positive responses are summed.

2 The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the Total score.

3 The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage:

$$\text{Score} = 100 \times \frac{\text{Summed weights from positive items in that component}}{\text{Sum of weights for all items in that component}}$$

The Total score is calculated in similar way:

$$\text{Score} = 100 \times \frac{\text{Summed weights from positive items in the questionnaire}}{\text{Sum of weights for all items in the questionnaire}}$$

The Symptoms component is calculated from the summed weights for the positive responses to questions 1-8.

The Activity component is calculated from the summed weights for the positive responses to questions 11 and 15.

The Impacts component is calculated from the summed weights for the positive responses to questions 9-10, 12-14 and 16-17.

The questionnaire requests a single response to questions 1-17. If multiple responses are given to one of these questions then averaging the weights for the positive responses for that question will be done.

The Total score is calculated by summing all positive responses in the questionnaire and expressing the result as a percentage of the total weight for the questionnaire.

Item weights

The wording of the item may not correspond exactly with the wording in the current version of the questionnaire.

PART 1

Response	Response weight
1) Over the past 4 weeks, I have coughed:	
Almost every day	80.6
Several days a week	63.2
A few days a month	29.3
Only with respiratory infections	28.1
Not at all	0.0
2) Over the past 4 weeks, I have brought up phlegm (sputum):	
Almost every day	76.8
Several days a week	60.0
A few days a month	34.0
Only with respiratory infections	30.2
Not at all	0.0
3) Over the past 4 weeks, I have had shortness of breath:	
Almost every day	87.2
Several days a week	71.4
A few days a month	43.7
Only with respiratory infections	35.7
Not at all	0.0
4) Over the past 4 weeks, I have had wheezing attacks:	
Almost every day	86.2
Several days a week	71.0
A few days a month	45.6
Only with respiratory infections	36.4
Not at all	0.0
5) How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?	
More than three times	86.7
3 times	73.5
2 times	60.3
1 time	44.2
None of the time	0.0
6) How long did the worst respiratory attack last?	
A week or more	89.7
3 or more days	73.5

Response	Response weight
1 or 2 days	58.8
Less than a day	41.9
7) Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?	
None of the days	93.3
1 or 2 days	76.6
3 or 4 days	61.5
Nearly every day was good	15.4
Every day was good	0.0
8) If you wheeze, is it worse when you get up in the morning?	
No	0.0
Yes	62.0

PART 2

Response	Response weight
9) How would you describe your respiratory condition?	
The most important problem I have	83.2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0.0
10) If you have ever held a job:	
My respiratory problems made me stop working altogether	88.9
My respiratory problems interfere with my job or made me change my job	77.6
My respiratory problems do not affect my job	0.0
Not applicable	0.0
11) These are questions about what activities usually make you feel short of breath these days.	
Sitting or lying still = TRUE	90.6
Washing or dressing yourself = TRUE	82.8
Walking around the house = TRUE	80.2
Walking outside on level ground = TRUE	81.4
Walking up a flight of stairs = TRUE	76.1
Walking up hills = TRUE	75.1
Playing sports or other physical activities = TRUE	72.1
12) These are more questions about your cough and shortness of breath these days.	
Coughing hurts = TRUE	81.1

Response	Response weight
Coughing makes me tired = TRUE	79.1
I am short of breath when I talk = TRUE	84.5
I am short of breath when I bend over = TRUE	76.8
My coughing or breathing disturbs my sleep = TRUE	87.9
I get exhausted easily = TRUE	84.0
13) Questions about other effects your chest trouble may have on you.	
My cough or breathing is embarrassing in public = TRUE	74.1
My respiratory problems are a nuisance to my family, friends or neighbors = TRUE	79.1
I get afraid or panic when I cannot catch my breath = TRUE	87.7
I feel that I am not in control of my respiratory problems = TRUE	90.1
I do not expect my respiratory problems to get any better = TRUE	82.3
I have become frail or an invalid because of my respiratory problems = TRUE	89.9
Exercise is not safe for me = TRUE	75.7
Everything seems too much of an effort = TRUE	84.5
14) These are questions about your respiratory treatment.	
My treatment does not help me very much = TRUE	88.2
I get embarrassed using my medication in public = TRUE	53.9
I have unpleasant side effects from my medication = TRUE	81.1
My treatment interferes with my life a lot = TRUE	70.3
15) These are questions about how your activities might be affected by your respiratory problems.	
I take a long time to get washed or dressed = TRUE	74.2
I cannot take a bath or shower, or I take a long time to do it = TRUE	81.0
I walk slower than other people my age, or I stop to rest = TRUE	71.7
Jobs such as household chores take a long time, or I have to stop to rest = TRUE	70.6
If I walk up one flight of stairs, I have to go slowly or stop = TRUE	71.6
If I hurry or walk fast, I have to stop or slow down = TRUE	72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf = TRUE	74.5

Response	Response weight
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim = TRUE	71.4
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports = TRUE	63.5
16) We would like to know how your respiratory problems usually affect your daily life.	
I cannot play sports or do other physical activities = TRUE	64.8
I cannot go out for entertainment or recreation = TRUE	79.8
I cannot go out of the house to do the shopping = TRUE	81.0
I cannot do household chores = TRUE	79.1
I cannot move far from my bed or chair = TRUE	94.0
17) Now please select the response (one only) that you think best describes how your respiratory problems affect you:	
It does not stop me from doing anything I would like to do	0.0
It stops me from doing one or two things I would like to do	42.0
It stops me from doing most of the things I would like to do	84.2
It stops me from doing everything I would like to do	96.7

Handling of missing items

The Symptoms component will tolerate a maximum of 2 missed items. The Activity component will tolerate a maximum of 4 missed items. The Impacts component will tolerate a maximum of 6 missed items. Domain score will be set to missing if there are more than tolerated number of items missing.

B 4 Calculation of BCSS scores

Table 29 BCSS© scoring

Item	Question	Score
Breathlessness	How much difficulty did you have breathing today?	0 – None 1 – Mild 2 – Moderate 3 – Marked 4 – Severe
Cough	How was your cough today?	0 – None 1 – Rare 2 – Occasional 3 – Frequent 4 – Almost constant
Sputum	How much trouble was your sputum today?	0 – None 1 – Mild 2 – Moderate 3 – Marked 4 – Severe

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