Clinical Study Protocol	
Study Intervention	MEDI3506
Study Code	D9180C00002
Amendment Number	5.0
Date	16 February 2022

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)

Sponsor Name:

AstraZeneca AB, 15185 Södertälje, Sweden

Regulatory Agency Identifier Numb r(s):

IND:147640

EudraCT number: 2020-000571-20

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

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Protocol Number: D9180C00002

Amendment Number: 5.0

Study Intervention: MEDI3506

Study Phase: Phase 2

Short Title: A Phase II, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of MEDI3506 in Participants with COPD and Chronic Bronchitis

Acronym: FRONTIER 4

Medical Monitor Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 5	16-Feb-202
Amendment 4	23-Jul-2021
Amendment 3	01-Jun-2021
Amendment 2	08-Feb-2021
Amendment 1	01-Oct-2020
Original Protocol	03-Jul-2020

Amendment 5 (16 February 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment:

To update the sample size and assumptions underlying its calculation and revise certain inclusion and exclusion criteria in response to investigator feedback.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Section 9.2 Sample Size Determination	Participants r ndomly assign d to study intervention and number of evaluable participants amended. Statistical methods section: Updated with new participant numbers and sample size justification.	After consideration of newly published clinical trial results (Rabe et al 2021) with another anti-IL-33 monoclonal antibody in COPD, the number of participants has been re-evaluated and updated.	Substantial
Section 1.3 Schedule of Activities.	Advice on spirometry assessment timing clarified.	To reduce the risk of a protocol deviation.	Non-substantial.
	Table 2 and Table 3 Salivary sample added as an additional option for the SARS-CoV-2 nucleic acid test.	To reflect latest procedures and provide an additional option to CCI [redacted]	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	CCI [redacted]	To minimise patient and site burden as baseline samples are collected at SV3	Non-substantial.
	CCI [redacted]	To minimise patient and site burden.	Non-substantial.
	Tables 2 and 3: Minor updates and reordering of footnotes	Consistency	Non-substantial.
Section 2.3.1 Risk Assessment, Table 4.	Updated risk assessment related to progression of heart failure.	To provide information based on current data.	Non-substantial.
Section 2.3.1 Risk Assessment, Table 4	CT risk mitigations revised.	The previously stated effective dose in mSv is not possible to determine accurately on an individual basis, but is still relevant on a population level. This is described in detail in the Radiology Manual. Target radiation exposure levels for the study have not changed.	Non-substantial.
Section 3 Objectives and Endpoints, Table 5.	CCI [redacted]	To simplify operational logistics.	Non-substantial.
	CCI [redacted]	Clarification	Non-substantial.
	CCI [redacted]	Correction	Non-substantial.
Section 4.1 Overall Design	Number of participants to be randomized has been updated and the expected percentage of participants in baseline and ICS strata removed	Consistency and to ensure that the final recruited population will more closely represent the eligible population.	Substantial
	Advice on ensuring adequate time for CT and echocardiogram assessments	To provide additional guidance	Non-substantial.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Use of eDiary and advice on spirometry assessment timing clarified.	To reduce the risk of a protocol deviation and consistency with other sections.	Non-substantial.
	Reduced overall number of patients in the CT sub study to remain proportionate to the reduced size of the main study.	To facilitate the sub study as optional and not a barrier to participation in the main study.	Non-substantial.
	When to perform echocardiogram in cases of suspected heart failure clarified.	Suspected heart failure should always be assessed irrespective of whether during an exacerbation or not.	Substantial
Section 4.1.2 Study Conduct Mitigation During Study Disruptions	CCI [redacted]	Service not available for this study	Non-substantial
Section 4.2 Scientific Rationale for Study Design	Details of monitoring the phenotype of participants removed.	To ensure that the final recruited population will more closely represent the eligible population.	Substantial
	Reduced overall number of patients in the CT sub tudy to remain proportionate to the reduced size of the main study.	To facilitate the sub study as optional and not a barrier to participation in the main study	Non-substantial
Section 5.1 Inclusion Criteria.	Criterion 1: Upper age limit chang d from 75 years to 80 years	Older age allowed as other exclusion criteria prevent those with significant comorbidities from being included in the study	Substantial
	Criterion 3 relating to vaccination removed and vaccination guidance included in concomitant medications (Section 6.5). Replaced with: This inclusion criterion has been removed.	To permit inclusion of patients who did not receive pneumococcal and influenza vaccination where recommended by local guidelines	Substantial.
	Criterion 4: Acceptable documentation for evidence of COPD and requirement to document updated.	Clarification of acceptable documentation.	Non-substantial
	Criterion 5: Lower limit for FEV_1 changed to 20%	To permit participation of patients with more severe	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		COPD who are otherwise potential treatment responders whilst excluding those with significant comorbidity or end-organ failure such as cor pulmonale or requiring LTOT	
	Criterion 8: Acceptable documentation for evidence of stable dual or triple therapy and requirement to document updated.	Clarification of acceptable documentation.	Non-substantial
	Criterion 9: Updated to confirmation by participant of self-administration of rescue medication for an acute exacerbation	Clarification of verbal confirmation and requirement to record in participant's source document	Non-substantial
	Criterion 13: Upper limit of body mass index increased to 40 mg/m^2	High r BMI allowed as other exclusion criteria prevent those with significant comorbidities from being included in the study	Substantial
Section 5.2 Exclusion Criteria, Medical Conditions and Diagnostic Assessments	Criterion 1: Rescreening allowed for participants with a positive diagnostic ucleic acid test for SARS-CoV-2	Clarification that participants with asymptomatic or mild disease are eligible.	Substantial
	Criterion 3a: Excepti n to exclusion from participation in study amended for diabetes mellitus	Clarification, and removal of HbA1c marker example.	
	Criterion 3c: Arrhythmia noted as including atrial fibrillation	Clarification	
	Criterion 3e revised to indicate systemic hypertension should be well controlled and stable for at least 3 months according to the investigator and remove the upper limit of two medications.	To include the need for investigator assessment and to reflect variation in global practice.	
	Criterion 3f revised to exclude clinically significant cor pulmonale	Clarification	

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Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Criterion 5: Reworded asthma exclusion criterion	Clarification	
	Criterion 9e removed and replaced with: This exclusion criterion has been removed	Redundant	
	Criterion 9g: Chest CT scan findings requiring surveillance revised	Clarification	
	Criterion 10: Removed and replaced with: This exclusion criterion has been removed	Based on high intra-patient variability nature of NT-proBNP in the COPD population, updated risk assessment (see IB for details) and presen e of other exclusion criteri ensure absence of heart failure in participants.	
	Criterion 15: Revised text related to LTOT	Simplification of text	
	Criterion 23: Revised text associated with hepatitis	Simplification of text	
	Criterion 24: Revised text associated with HIV	Clarification	
Section 5.2 Exclusion Criteria, Prior Therapy	Criterion 34h: Re ised to allow chronic macrolide or other antibiotic therapy provid d criteria re met	Consistency with product development program	Non-substantial
	Criterion 34i: Examples of PDE4 inhibitors added and guidance revised to allow PDE4 inhibitors provided criteria are met	Consistency with product development program	
	Criteria 34k, and l: Updated and aligned with Section 6.5.5	Clarification and consistency	
Section 5.2 Exclusion Criteria Other Exclusions	Criterion 41: Removed as there is no longer capping of strata	Clarification.	Non-substantial
Section 5.2 Exclusion Criteria for Imaging Sub study	CCI [redacted]	CCI [redacted]	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.3.1 Methods for Assigning Study Intervention Groups	Removal of text around strata caps and safety alerts	To align with Section 5 and correction	Non-substantial
Section 6.3.2 Methods to Ensure Blinding	Removal of text on safety alerts for certain hematology tests	Alerts not necessary	Non-substantial
Section 6.5 Concomitant Therapy	Vaccination against influenza and pneumonia advice revised.	To permit inclusion of patients who did not receive pneumococcal and influenza vaccination where recommended by local guid lines	Substantial
Section 6.5.5 Restricted and Prohibited Medications	Revised text related to Macrolide therapy and LTOT	Simplifica ion of text and alignment with Section 5.2	Non-substantial
	Baseline audiometry testing required to be documented before randomisation.	To ensure safety of participants during study participation. There is an identified risk of macrolides causing ototoxicity.	Substantial
Section 8.1.3 Home Spirometry and eDiary	Advice on spirometry assessment timing clarified.	To reduce the risk of a protocol deviation and consistency with other sections.	Non-substantial.
	Added text on importance of transmitting data daily	To emphasise the need for this to be done	
CCI	CCI	CCI	CCI
Section 8.5.2 Immunogenicity Assessments	Revised text to add circumstances in which ADA samples might be collected after the follow up period	Clarification	Non-substantial
Section 9.2 Sample Size Determination	CCI	To reflect the expectation of determining an effect in a smaller sample of 20 patients per arm.	Non-substantial
Section 9.4.2.2 Subgroup Analyses	Removed numerical range for extent of emphysema	Redundant, will be described in the SAP	Non-substantial

ADA = Anti-drug antibody(ies); BMI = Body mass Index; COPD = Chronic obstructive; pulmonary disease; CT = computer tomography; FEV_1 = Forced expiratory volume in 1 Second; HbA1c = glycated haemoglobin; IB = Investigators' Brochure; IL-33 = Interleukin 33; LTOT = Long term oxygen therapy; NT-proBNP = N-terminal pro-brain natriuretic peptide; PDE4 = Phosphohipidesterase-4; SAP = Statistical analysis plan; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; CCI [redacted] SV = Study visit.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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)

Short Title: A Phase II, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of MEDI3506 in Participants with COPD and Chronic Bronchitis

Rationale: The purpose of this proof-of-concept study is to evaluate the efficacy, safety and tolerability of MEDI3506 in participants with COPD and Chronic Bronchitis.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effects of MEDI3506 compared with placebo on pulmonary function in participants with COPD and chronic bronchitis.	Cha g from baseline to Week 12 in pre-BD FEV_1 measured in clinic.
Secondary	
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 participant 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

Objectives	Endpoints
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
Safety	
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. • Fo participants testing positive for SARS-CoV-2 (by nucleic acid or serology test), during the intervention and follow-up periods, the number and proportion of participants 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 ev of special interest; AO = Airwave oscillometry; AX = Area of reactance; BCSS = Breathlessness, cou and sputum scale; BD = Bronchodilator; COPD = Chronic obstructive pulmonary disease; COVID-19 = Cor disease 2019; COPDCompEx = COPD Composite Exacerbations; ECG = Electrocardiogram; E-RS:COPD = Eva ting Respiratory Symptoms of COPD; FEV_1 = Forced expiratory volume in 1 second; FVC Forced Vital Capacity; LVEF = Left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natri etic peptide; PK = Pharmacokinetic; R5 = Resistance at 5Hz; R20 = Resistance at 20 Hz; SAE = Serio verse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St. Ge ge's Respiratory Questionnaire; VAS = Visual analogue scale.

For Exploratory objectives and endpoints, see Section 3 of the CSP.

Overall Design

This is a Phase II, randomized, double-blind, placebo-controlled, proof-of-concept study to assess the efficacy, safety, and tolerability of MEDI3506 in participants with moderate or severe COPD receiving Standard of Care (dual or triple therapy) as maintenance therapy. Participants also have 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.

Participants will be enrolled for at least a 4-week screening/run-in period, a 28-week intervention period (during which they receive 7 doses SC Q4W), and an 8-week follow-up period.

Participants must be on stable doses of dual therapy (ICS + LABA, or LABA + LAMA) or triple therapy (ICS + LABA + LAMA) for ≥ 3 months prior to enrolment and should remain so during the study. There should have been no change in maintenance COPD treatment after a previous exacerbation prior to entering into the study.

There is one sub-study included as part of the trial: CCI [redacted].

Disclosure Statement: This is a parallel group treatment study with 2 arms (MEDI3506 and placebo) that is participant, investigator, and sponsor blinded.

Number of Participants:

Approximately 144 participants will be randomly assigned to study intervention (MEDI3506 or placebo) such that approximately 140 participants are evaluable for the primary analysis.

Intervention Groups and Duration:

All participants passing the initial screening visit will enter a run-in period of at least 4 weeks on their usual standard of care treatment. Participants will be randomized to MEDI3506 or placebo if they continue to meet all eligibility criteria, including adherence to home assessments and spirometry criteria using data from the run-in period.

Approximately 144 participants will be randomized 1:1 to MEDI3506 CCI [redacted] SC Q4W or placebo for 7 doses.

Data Monitoring Committee:

A DSMB has been established to oversee the MEDI3506 clinical development program. In addition to a full DSMB 6-month periodic review of safety data, the DSMB chair will review unblinded safety data summaries every 3 months; the DSMB can meet on an ad hoc basis. A blinded study-specific safety committee (or Medical Monitor) will also review SAEs and SUSARs.

Statistical Methods:

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 of 90 mL (assumed standard deviation of 250 mL) between the two 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).

Statistical Analyses:

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, 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. 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. An unstructured covariance matrix will be used to describe the correlations between observations on a participant between visits.

A similar approach will be taken for the analysis of cough VAS, BCSS, CCI SGRQ, and CCI. Data may be log-transformed prior to analysis where appropriate. Change from baseline in objective cough parameters and oscillometry parameters at Week 12 will be analyzed using analysis of covariance.

Analysis of time to event CCI will include available data (up to Week 28 where this is available) for all participants. Time to event endpoints will be analyzed using a Cox proportional hazards model.

Safety endpoints including AEs, SAEs, AESIs, laboratory parameters, vital signs, ECGs, and physical examinations will be summarized using descriptive statistics.

1.2 Schema

The general study design is summarized in Table 1.

Table 1 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.

Participants will receive 7 administrations of study intervention Q4W. SV12 (Week 28) will serve as the end of intervention visit (see Section 4.1). The primary endpoint visit occurs at SV8 (Week 12).

1.3 Schedule of Activities

Patient reported outcome questionnaires to be completed at site visits must be completed prior to study intervention administration and ideally before any discussions of health status or other study procedures, such as collection of laboratory samples, to avoid biasing the participant's responses to the questions. All daily ePRO assessments for the morning and evening eDiary at home should be completed within the set time window programmed into the device; device alerts will notify the participant when it is time to respond to the questions. After each study visit, participants will return to the normal schedule of answering the eDiary at home.

Order of procedures:

- All assessments should be performed prior to administration of investigational product except where otherwise indicated (eg, post-dose vital signs)
- Participants will be instructed to perform all home spirometry assessments before use of their usual standard-of-care inhaled medication. Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the order should be as follows: ECG, vital signs (vital signs can occur immediately after ECG using the same rest period), then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the assigned nominal time.
- AO assessments should take place before spirometry.
- Sputum samples should be taken after procedures requiring a BD withhold (including spirometry and AO).
- If both nasal epithelial lining fluid and mucosal samples are required on the same day then the epithelial lining fluid sample should be taken prior to the mucosal sample.

Refer to Section 8 for additional information on assessment ordering (eg, pre-, post-dose or multiple timepoints within a visit).

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Table 2 Screening Procedures

Study Period	Screening / Run-in	
Visit Number	**SV1**	**SV2**
Procedure / Study Day	**Day -35 to Day -28**	**Day -21 to Day -7**
Study Week	**Week -5 to -4**	**Week -3 to -1**
Written informed consent/assignment of E-code [a]	X	
Written informed consent for future use and/or genetic analysis (optional) [a]	X	
Written informed consent for CT sub-study (as applicable) [a]	X	
Verify eligibility criteria	X	X
Safety Assessments		
Demography	X	
Medical and COPD/chronic bronchitis history including assessment of COPD exacerbations and evaluation of predominant emphysema by physician diagnosis	X	
Smoking History	X	
Physical examination (full)	X	
Weight, height	X	
ECG	X	
Vital signs	X	
Assessment of AEs/SAEs	X	X
Concomitant medications	X	X
Echocardiogram [a, b]		X
CT [a, b, c]		X
SARS-CoV-2 nucleic acid test (nasopharyngeal swab or salivary sample) [d]	X	X
Efficacy assessments		
Clinic Spirometry (pre-BD)	X	
Clinic Spirometry (post-BD)	X	
Airwave oscillometry		X
Provision, and training on use, of at home spirometer and eDiary for use every day	X	
Assess adherence to the completion of eDiary entries and home device use		X
Provision of and training of use of cough monitoring **followed by 24 hour monitoring post clinical visit**		X

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Table 2 Screening Procedures

Study Period	Screening / Run-in	
Visit Number	**SV1**	**SV2**
Procedure / Study Day	**Day -35 to Day -28**	**Day -21 to Day -7**
Study Week	**Week -5 to -4**	**Week -3 to -1**
On-site ePROs:		
CAT	X	
Collect blood for:		
Serum chemistry	X	
NT-proBNP	X	
Haematology	X	
Coagulation parameters	X	
Hepatitis B, C; HIV-1; virology	X	
Serum pregnancy test (female participants of childbearing potential only)	X	
FSH (if needed to confirm post-menopausal status in female participants aged < 50 years)	X	
IGRA (TB test)	X	
Collect other samples:		
CCI [redacted]		
Collect urine for:		
Urinalysis	X	
Pregnancy test (female participant of childbearing potential only) [f]		X
CCI [redacted]		
See CT scan collected as part of the safety assessments above		
Pandemic impact assessment	X	X

CCI [redacted]

[b] Echocardiogram and CT dates will be scheduled at SV1, to occur post-confirmation of eligibility at SV2.

CCI [redacted]

[d] May be performed on a separate day ahead of study visit if required. The analysis can either be performed locally or centrally.

CCI [redacted]

[f] Only required if a CT scan as part of SV2 is performed. If required must be done prior to CT scan.

AE = Adverse event; BD = Bronchodilator; CAT = COPD assessment test; COPD = Chronic obstructive pulmonary disorder; CT = Computed tomography; ECG = Electrocardiogram; ePRO = Electronic patient reported outcomes; FEV_1 = Forced expiratory volume in 1 second; FSH = Follicle stimulating hormone; HIV = Human immunodeficiency disease; IGRA = Interferon gamma release assay; NT-proBNP = N-terminal pro-brain natriuretic peptide; PEF = Peak expiratory flow; SAE = Serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St George's Respiratory Questionnaire; SV = Study visit; TB = Tuberculosis.

Table 3 Schedule of Activities: Study Intervention and Follow-up

Study Period	**Intervention Period**										**Follow-up**			
Visit Number	**SV3**	**SV4 TC**	**SV5**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**SV13**	**SV14**		
Study Day (SV5 to SV14 window: ± 3 days)	**1**	**2**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**		
Study Week	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**E/D**	**E/A** [a]
Efficacy assessments														
Clinic spirometry (pre-BD)	X		X	X	X	X	X	X	X	X	X	X	X	
Clinic spirometry (post-BD)						X				X			X	
Airwave oscillometry	X					X				X			X	
Use of at home spirometry [b] and eDiary [c]	Every day throughout intervention and follow-up periods													
Assess adherence to the completion of eDiary entries and home device use (including PEF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cough monitoring (24 hour monitoring post clinic visit)						X								
CCI														
ePRO: SGRQ	X			X		X				X			X	
CCI														
Study Participant Feedback Questionnaire (Optional)	X					X						X	X	
Assessment of COPD exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments														
Physical examination [a, c]	X		X	X	X	X	X	X	X	X	X	X	X	X
Weight	X					X				X			X	
ECG	X					X				X		X	X	
Vital signs [d]	X		X	X	X	X	X	X	X	X	X	X	X	

Table 3 Schedule of Activities: Study Intervention and Follow-up

Study Period	Intervention Period										Follow-up			
Visit Number	**SV3**	**SV4 TC**	**SV5**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**SV13**	**SV14**		
Study Day (SV5 to SV14 window: ± 3 days)	**1**	**2**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**		
Study Week	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**E/D**	**E/A [a]**
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echocardiogram [e]						X [f]				X [f]				
Injection site reactions	X	X	X	X	X	X	X	X	X	X			X	
Nasopharyngeal swab or salivary sample for SARS-CoV-2 nucleic acid test [g]	X		X	X	X	X	X	X	X	X	X	X	X	
Collect blood for														
Serum Chemistry	X		X	X		X		X		X	X	X	X	
CCI														
CCI														
CCI														
CCI														
NT-proBNP [e]						X				X			X	
Haematology	X		X	X		X		X		X	X	X	X	
PK	X		X	X		X		X	X	X	X	X	X	
Immunogenicity	X		X	X		X		X	X	X	X	X	X	
CCI														
Genetic analysis (optional)	X [i]													
SARS-CoV-2 serology test (serum)	X					X				X			X	

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Table 3 Schedule of Activities: Study Intervention and Follow-up

Study Period	Intervention Period										Follow-up			
Visit Number	**SV3**	**SV4 TC**	**SV5**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**SV13**	**SV14**		
Study Day (SV5 to SV14 window: ± 3 days)	**1**	**2**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**		
Study Week	**0**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**E/D**	**E/A** [a]
Collect urine for														
Urinalysis	X			X		X				X			X	
Pregnancy test (female participants of childbearing potential only)	X			X	X	X	X	X	X	X		X	X	
Collect other samples														
CCI														
Nasal epithelial lining fluid	X			X	X	X		X		X		X		
CCI														
CCI														
CCI										CCI				
Verify eligibility criteria	X													
Randomization	X													

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Table 3 Schedule of Activities: Study Intervention and Follow-up

Study Period	Intervention Period										Follow-up			
Visit Number	SV3	SV4 TC	SV5	SV6	SV7	SV8	SV9	SV10	SV11	SV12	SV13	SV14		
Study Day (SV5 to SV14 window: ± 3 days)	1	2	15	29	57	85	113	141	169	197	225	253		
Study Week	0	0	2	4	8	12	16	20	24	28	32	36	E/D	E/A [a]
Study intervention administration [m]	X			X	X	X	X	X	X					
Pandemic Impact Assessment [n]	X		X	X	X	X	X	X	X	X	X	X	X	

[a] Additional assessments may be performed as clinically indicated

[b] Participants will be instructed to perform all home spirometry assessments before use of their usual standard-of-care inhaled medication

[c] Brief physical examination, except at SV3 (Day 1) and E/D where a full physical examination is required.

[d] Assessments at multiple time points refer to Section 8.2.3.

[e] Also performed when new onset heart failure is suspected, or as soon as possible thereafter.

[f] May be performed at any time during preceding 4 weeks.

[g] May be performed on a separate day ahead of study visit if required. Testing may be performed at any point for a participant suspected of having COVID-19. This test can either be performed locally or centrally. A less demanding schedule of testing may, in certain circumstances, be authorised by the medical monitor, see Section 8.2.6.

CCI

[i] If not taken at SV3 may be taken at any subsequent visit.

CCI

CCI

If not successfully collected, a second attempt should be conducted on a subsequent day, but no more than 7 days after the nominal study day.

[m] If a suspected anaphylactic reaction occurs during or within a 24-hour period after administration of study intervention, blood samples for serum tryptase will be collected as soon as possible after the event, at 60 ± 30 minutes after the event, at discharge, and between 2 and 4 weeks post discharge. Immediate care of the participant and treatment of the reaction must take priority over collecting blood samples. For additional details on anaphylactic reactions see Appendix I.

[n] For COVID-19 mitigation, please see Section 4.1.1.

Note: Study procedures should take place prior to dosing, unless specified otherwise (eg, for collection of vital signs).
AE = Adverse event; BD = Bronchodilator; CCI COPD = Chronic obstructive pulmonary disorder; COVID-19 = Coronavirus disease 2019; CCI CT = Computed tomography; d = day; ECG = Electrocardiogram; E/A = Exacerbation Assessment; E/D = Early Study Intervention Discontinuation Visit; CCI NT-proBNP = N-terminal pro-brain natriuretic peptide; PEF = Peak expiratory flow; CCI PK = Pharmacokinetic; ePRO = Electronic patient-reported outcome; SAE = Serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SGRQ = St George's Respiratory Questionnaire; SV = Study Visit; TC = Telephone contact.

2 INTRODUCTION

MEDI3506 is a human IgG1 mAb that binds to human IL-33, which is being developed for the treatment of asthma, atopic dermatitis, COPD, and diabetic kidney disease.

2.1 Study Rationale

The MEDI3506 pre-clinical profile suggests that MEDI3506 can reduce airway inflammation, improve epithelial integrity, reduce mucus production, and improve muco-ciliary transport. As such, MEDI3506 is hypothesized to impact COPD status by increasing FEV_1 (and other physiological measures of lung function) and reducing frequency and severity of COPD exacerbations, thereby improving quality of life.

One Phase I clinical study of MEDI3506 (Study D9180C00001) was completed in December 2019. Study D9180C00001 was a first-in-human, randomized, placebo-controlled, blinded (investigator and participant blinded; sponsor unblinded) clinical study in 88 participants to evaluate the safety, tolerability, PK and immunogenicity of single and repeated doses of MEDI3506. MEDI3506 was generally found to be safe and well tolerated. For further details refer to the IB.

The purpose of this proof-of-concept study is to evaluate the safety and efficacy of MEDI3506 in participants with COPD and chronic bronchitis.

2.2 Background

Chronic obstructive pulmonary disease is the fourth leading cause of death in the world and is projected to be the third leading cause of death worldwide by 2030 (Adeloye et al 2015). Chronic obstructive pulmonary disease is characterized by persistent respiratory symptoms and airflow limitation (post-BD $FEV_1/FVC < 0.70$) that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases, and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality (GOLD 2020). Chronic obstructive pulmonary disease is not fully reversible, usually progressive and associated with an enhanced chronic inflammatory response in the lung. Patients with active chronic bronchitis symptoms bear a greater burden of disease than those without and are characterized by more rapid loss of lung function, increased mortality and increased risk of exacerbation (Kim et al 2011; de Oca et al 2012; Corhay et al 2013; Kim and Criner 2013; Woodruff et al 2016; Lahousse et al 2017). Mucus hypersecretion with accumulation in the small airways in COPD is present independent of symptoms of cough and sputum production (Caramori et al 2004; Burgel and Nadel 2008) and can coexist with extensive emphysema (Dunican et al 2021; Kim et al 2021). Mucus plugging is evident at all stages of severity of COPD, but is greatest in those with most severe disease. The correlation between extent of emphysema and mucus plugging is not well defined but both independently negatively correlate with FEV_1. Patients

with recurrent COPD exacerbations have higher sputum inflammatory markers (Bhowmik et al 2000) which suggests that underlying inflammation may lead to disease progression (Crooks et al 2000; Anzueto 2010). Interleukin-33 expression is upregulated in the lungs of patients with COPD, is inversely correlated with lung function, and has a role in inflammatory and epithelial processes in COPD.

MEDI3506 is a mAb that binds to IL-33 and potently and specifically blocks all forms of IL-33 to prevent their signalling. Interleukin-33 is an alarmin cytokine from the IL-1 family. Interleukin-33 is localized in the nucleus, and following injury, stress or cell death, it is released from the cell, and exerts a pro-inflammatory biological function, which is skewed towards a pro-inflammatory Th1 cytokine profile and broad responder cell population on the background of smoke-induced inflammation (Kearley et al 2015). Interleukin-33 pathway blockade prevents exacerbation of viral-induced inflammation in a mouse smoke exposure model (Kearley et al 2015), and IL-33 has been shown to have a role in goblet cell hypertrophy, mucus hypersecretion and the ratio of mucus producing to ciliated cells in airway epithelium in mouse models of prolonged lung inflammation (Schmitz et al 2005; Allinne et al 2019). As such, MEDI3506 mode of action is hypothesized to impact airway inflammation, mucus and cough symptoms and lung function endpoints in COPD, and through modification of these factors, reduce frequency and severity of exacerbations. This proposed mode of action of MEDI3506 suggests that COPD patients with chronic bronchitis may be most likely to gain benefit from MEDI3506 treatment, and therefore COPD participants with chronic bronchitis are an appropriate population to begin efficacy testing of MEDI3506.

A detailed description of the chemistry, pharmacology, mechanism of action, and safety of MEDI3506 is provided in the IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of MEDI3506 may be found in the IB.

2.3.1 Risk Assessment

To date, there are no identified risks associated with MEDI3506. Potential risks for MEDI3506 are described in Table 4 and in more detail in the IB.

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
MEDI3506		
Gastrointestinal adverse reactions	Observation of what was considered an incidental finding of ulcerative colitis in the 26-week toxicity study in cynomolgus monkeys (see IB Section 4.3.1.2). The gastrointestinal effects of IL-33 blockade in humans are currently unclear. IL-33 is expressed in the gastrointestinal tract, where it has multiple downstream effects (Hodzic et al 2017). Expression of IL-33 is elevated in patients with active ulcerative colitis.	• Exclusion criteria 3(h), 13 and 30 • See Section 7.1 for a description of withdrawal criteria • Routine blinded review of the safety data for treatment-emergent gastrointestinal AEs • See IB Section 5.5.1.1
Serious infections (including opportunistic infections and viral reactivations)	Mechanism of action of MEDI3506 in particular, the role of IL-33 as an "epithelial alarmin" (Martin and Martin 2016)	• Exclusion criteria 3(g), 13, 20, 23, 24, 25, 30 and 34(a)-34(e) • See Section 7.1 for a description of withdrawal criteria • Routine blinded review of the safety data for serious and/or opportunistic infections by duration of study intervention • See IB Section 5.5.2.1
Progression of heart failure	Certain scientific data exists linking both IL-33 and its CCI CCI to heart failure. However, interpretation is complicated (see IB Section 5.5.2.2 for details), hence, the relationship between CCI levels and local IL-33 activity remains unclear.	• Exclusion Criteria 3(a)-3(f), 9(d), 9(f), 11, 12 and 28 • Additional monitoring via echocardiograms and NT-proBNP • See Section 7.1 for a description of withdrawal criteria • Routine blinded review of the safety data of cardiac events by duration of study intervention • See IB Section 5.5.2.2
Injection-site reactions	This is based on the SC route of administration and the nature of MEDI3506 as an exogenous protein substance.	• Instructions on injection technique including rotation of injection sites. • Routine monitoring for injection site assessments will be undertaken at each visit. • Routine blinded review of the safety data for appearance of injection site reactions • See IB Section 5.5.3.1

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Serious hypersensitivity (including Type 1 to 4 hypersensitivity reactions) and Immune Complex Disease	As mAbs are foreign proteins they have the potential to provoke hypersensitivity reactions. Based on a potential risk known to be associated with foreign proteins, occurrence of ADAs could result in immune complex disease.	• Exclusion Criteria 8, 19, and 32 • Routine blinded review of the safety data, including anaphylactic symptoms • Required monitoring of participants for a minimum of 1 to 2 hours after study intervention administration Sites should be trained to recognise, and equipped to manage, anaphylaxis and serious allergic reactions until the participant can be transferred to a suitable facility (see Appendix I) • See IB Section 5.5.4.1
Reproductive toxicity	Consistent with ICH guidance on the timing of nonclinical studies, MEDI3506 has not been evaluated in embryo-fetal development toxicity studies	• Stipulation of highly effective contraceptive requirements for participants • Inclusion Criteria 14, 15, 16 • See IB Section 5.5.5.1
Study Procedures		
CCI [redacted]	Temporary, mi or discomfort (similar to drawing blood).	• To be performed by appropriately trained staff. • If deemed by the investigator to be intolerable for individual participant at SV3 (eg, due to nasal polyps), subsequent assessments may be omitted (see Table 3).

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Ionising radiation from CT	Low dose CT scans will be performed for the purpose of investigating the impact of the extent of emphysema on CT scan on the effect of the study intervention on clinical endpoints, and to measure the effect of the study intervention on the airways in a subset of participants. The ionising radiation from low dose CT may cause a very small increased risk of developing cancer in participants who also may have an elevated risk of cancer due to smoking history.	• Participants will be informed of the risks associated with CT before entering the study. In keeping with the as low as reasonably achievable concept (ALARA), the trial uses optimized CT scan protocols, utilizing the lowest possible radiation dose to each participant in order to provide acceptable image quality for the quantitative measurements performed in the study. For more detailed information related to CT radiation dose, imaging risks, and best imaging practices, please refer to the study Radiology Manual. CCI [redacted]
Aerosol generation from certain study procedures	Forced sp r metry m y generat aerosols with risk of spreading respira ory infectious disease. Risk to staff and other participants nearby, rather than participant undergoing procedure.	• Usual infection control measures should be followed during procedures, including use of filters during forced spirometry, per the instructions of the central vendor. • Any additional infection control measures in accordance with COVID-19 related local and national guidelines should also be followed.

ADA = Anti-drug antibody; AE = Adverse events; COVID-19 = Coronavirus disease 2019; CT = Computed tomography; IB = Investigator's Brochure; ICH = International Council for Harmonization; IL-33 = Interleukin-33; mAbs = Monoclonal antibodies; CCI [redacted]
NT-proBNP = N-terminal pro-brain natriuretic peptide; SC = Subcutaneous; CCI [redacted] SV = Study Visit.

As per above, serious infections (including those with SARS-CoV-2) are also a potential risk of MEDI3506. AstraZeneca is not aware of any current evidence of a direct link between IL-33, or IL-33 suppression, and contracting SARS-CoV-2 and early stages of COVID-19 illness post infection. Moreover, it is hypothesised that IL-33 suppression might be beneficial in the later, hyperinflammatory phase of severe COVID-19 illness; MEDI3506 will be tested in patients with severe COVID-19 infections as part of the ACcelerating COVID-19 Research and Development (ACCORD) Study 2 (ACCORD-2; EudraCT number 2020-001736-95).

2.3.2 Benefit Assessment

The purpose of this proof-of-concept study is to evaluate the safety and efficacy of MEDI3506 in participants with COPD and chronic bronchitis. For participants randomized to MEDI3506, there is a potential benefit in terms of improvement of their COPD disease status and reduction in COPD exacerbations. However, since at this early stage of clinical development, it is yet to be determined if MEDI3506 has an effect in patients with COPD with chronic bronchitis, participants might not receive any individual benefit from participating in this study. Participants will be required to continue all their COPD maintenance treatment throughout the study to minimize the risk of disease status worsening during the study.

To date, efficacy of MEDI3506 has not been assessed in patients with COPD and, hence, there are no clinical data that show benefit in this population. However, safety data obtained during Phase I in participants with COPD and the pre-clinical scientific data support clinical development of MEDI3506 in COPD.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with MEDI3506 are justified by the anticipated benefits that may be afforded to participants with COPD with chronic bronchitis.

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints

Objective	Endpoint
Primary	
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.
Secondary	
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
Safety	
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.

PPD

Table 5 Objectives and Endpoints

Objective	Endpoint
	• ECGs. • LVEF as measured by echocardiogram. • NT-proBNP. • For participants testing positive for SARS-CoV-2 (by nucleic acid or serology test), during the intervention and follow-up periods, the number and proportion of participants 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.
Exploratory	
CCI	[redacted]

Table 5 Objectives and Endpoints

Objective	Endpoint
CCI	

Table 5 Objectives and Endpoints

Objective	Endpoint
CCI	
Exploratory Sub-study	
CCI	

AE = Adverse event; CCI AESI = Adverse event of special interest; AO = Airwave oscillometry; AX = Area of reactance; BCSS = Breathlessness, cough and sputum scale; BD = Bronchodilator; CCI COPD = Chronic obstructive pulmonary disease; CompEx = Composite Exacerbations; COVID-19 = Coronavirus disease 2019; CCI CT = Computed tomography; CCI ECG = Electrocardiogram; E-RS:COPD = Evaluating Respiratory Symptoms of COPD; FEV_1 = Forced expiratory volume 1 second; FVC = Forced vital capacity; IL = Interleukin; LVEF = Left ventricular ejection fraction; CCI NT-proBNP = N-terminal pro-brain natriuretic peptide; PD = Pharmacodynamics; CCI PK = Pharmacokinetic; R5 = Resistance at 5Hz; R20 = Resistance at 20 Hz; SAE = Serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St. George's Respiratory Questionnaire; CCI CCI VAS = Visual analogue scale.

PPD

4 STUDY DESIGN

4.1 Overall Design

For an overview of the study design see Table 1. For details on study interventions given during the study, see Section 6. For details on what is included in the efficacy and safety endpoints, see Section 3. For further details on assessments, including screening assessments, see Section 8.

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).

Improvement in FEV_1 (primary endpoint) is considered important but not sufficient to show the potential of MEDI3506 to meet the unmet medical need in COPD. Therefore, COPDCompEx (secondary endpoint) will be used to assess whether MEDI3506 has wider clinical efficacy, specifically, that treatment with MEDI3506 has the potential to reduce acute exacerbations. To enable evaluation of COPDCompEx, an intervention period of 28 weeks (7 doses) has been selected (see Section 4.2.3).

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 [redacted] and background medication (includes ICS vs does not include ICS).

There are 3 study periods: screening and run-in; intervention period; and follow-up (Table 1).

Screening/Run-in Period

Informed consent and evaluation of inclusion/exclusion criteria (with the exception of CT, echocardiogram measures, and eDiary compliance) will be assessed at SV1. Only participants who meet all other eligibility criteria will be required to perform echocardiogram, CT and other scheduled assessments at screening SV2. Echocardiogram and CT dates will be scheduled at SV1, to occur post-confirmation of eligibility at SV2. SV1 and SV2 may be conducted over more than one clinic appointment to accommodate informed consent, echocardiogram, CT and sputum assessments; however, these must be completed in accordance with the SV window, per Table 2, and to allow sufficient time for a radiologist review prior to SV3 (Randomization Visit).

At the completion of initial enrolment at SV1, participants will proceed to the run-in period for at least 4 weeks, to allow adequate time for all the eligibility criteria to be evaluated. At approximately 1 to 3 weeks into the study period, SV2 will be conducted to further assess participant eligibility, including CT assessment of emphysema and echocardiogram. Sites should ensure there is adequate time to ensure results of CT and echocardiogram are available to determine eligibility. Computed tomography emphysema percentage will be calculated using automated software by an external vendor. Where an automated report is not possible due to technical issues, if possible, the CT scan emphysema percentage will be reported by a suitably qualified radiologist provided by the external vendor. Moreover, a suitably qualified radiologist at the clinic site (for clinical findings outside of emphysema and morphometric assessment) will be required to review the CT for additional findings, before SV3.

Presence or absence of excessive improvement in FEV_1 will be assessed between SV1 and SV3 (period of at least 4 weeks). Acceptable adherence of eDiary completion, at-home assessments, and BCSS average score in cough and sputum domains will be assessed over the 14 days preceding SV3. Participants who meet the eligibility criteria will be randomized to study intervention.

During the screening period, the participant must undergo all assessments per Table 2 including biosampling and baseline CT evaluation, with the exception of blood sampling for genomic assessments, which is optional. A previously performed chest CT scan may be acceptable for baseline evaluation, see Section 8.1.9.

Participants will be given a device at SV1, incorporating a spirometer for PEF/FEV_1 and an eDiary for recording symptom and medication use including as-needed medication at home. This will be used to collect baseline data of spirometry, the eDiary (ER-S:COPD, BCSS, cough VAS item), and adherence during the screening/run-in period (at least 4 weeks). Participants will be instructed to perform all home spirometry assessments before use of their usual standard-of-care inhaled medication.

Participants entering the sub-study CCI [redacted] will have additional requirements during the screening period as set out in Section 8, as long as sub-study eligibility is confirmed for the individual participants. Sub-study participation is dependent on site expertise / capability.

CCI [redacted]

Participants will continue with stable doses of permitted concomitant COPD medications from the screening through to the randomization visit.

Intervention Period: 7 doses and EOT visit

Section 6.5.5 provides a list of medication restrictions and prohibitions to be followed throughout the conduct of the clinical trial.

A DSMB has been established to oversee the MEDI3506 clinical development program. Further details of the DSMB are found in Section 9.6.

Participants will be maintained on their currently prescribed maintenance therapies from enrolment throughout the run-in, intervention period and follow-up period. During the intervention period, the participant must undergo all assessments per Table 3, with the exception of blood sampling for genomic assessments which is optional, and repeat CCI [redacted] which is at the investigator's discretion as detailed in Section 8.6.1.2.

Intervention Period

Participants fulfilling all eligibility criteria, including those requiring a review of data gathered at SV2 assessment and SV3 pre-dose, will begin a randomized, placebo-controlled intervention period of 7 doses. The primary endpoint assessment occurs at Week 12. The final dose is administered at Week 24. The End of Intervention visit is at Week 28. MEDI3506 or placebo will be administered by SC injection Q4W.

Participants will be reviewed by a telephone visit after first dose visit and attend on site visits to perform assessments including blood sampling, spirometry and other functional measurements such as AO, as per the SoA (Section 1.3).

Participants will remain at the investigational site:

- After the first and second dose of study intervention: At least 2 hours post dose for observation; or until participant is stable; or the time taken to complete SoA, whichever is longest
- After Doses 3, 4, 5, 6 and 7: At least 1 hour post dose for observation; or until participant is stable; or the time taken to complete SoA, whichever is longest

Participants will be asked to complete the eDiary, home spirometry. In addition, all participants will be asked to wear a cough monitoring device for 24 hours immediately following study visits as per SoA (Section 1.3).

An automated alert will be provided to the participant and site if there is a significant deterioration in the eDiary data points, prompting the participant to contact the site or their treating physician for further clinical review and management of a possible AECOPD.

At clinic visits, participants will undergo a short assessment to confirm moderate or severe AECOPD including assessments of appropriate management.

CCI

[redacted]

Follow up Period

Follow-up visits will occur 4 and 8 weeks after EOT visit to allow for determination of immunogenicity and potential prolonged PD effects, and evaluation of safety. Participants will be discharged from follow-up 3 months after the last dose of study intervention.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL in 3 months. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Additional Visits

A clinical assessment of any potential exacerbation during the intervention and follow up periods will occur either at the next scheduled visit or, if necessary, an additional E/A visit prior to the next scheduled visit (see the SoA in Section 1.3).

For any participants with suspected heart failure during participation in the study, an ad hoc echocardiogram and NT-proBNP measurements are required. In addition, for these participants, vital signs, physical examinations and any other examinations (eg, chest X-ray) can be performed at the investigator's discretion, following local standard practice.

4.1.1 Study (and Sub-Study) Conduct and Planned Mitigations During COVID-19 Pandemic

Coronavirus disease 2019 has emerged as a worldwide pandemic disease with significant implications for public health. AstraZeneca accepts that a careful risk-benefit analysis should be performed in each region before initiating clinical research that impacts the clinical resources needed for the COVID-19 pandemic. Hence, AstraZeneca will monitor countries and sites, and the study will not begin until local and national governments and clinical sites have indicated that it is acceptable to conduct clinical studies, any stay-in-place or lockdown orders have been lifted, and the safety of site staff and participants can be ensured. Furthermore, each study site must have appropriate measures to ensure safety of site staff and participants.

It is recognised that depending on the location and facilities of a clinical site, study visit attendance may place participants at risk of exposure to SARS-CoV-2. Where visits need to occur at locations other than the primary study site (eg, CT scans or echocardiograms), then

the investigator should select appropriate locations given the current environment. It is accepted that additional visits (eg, as part of CCI participation) necessarily entail an additional risk of exposure to SARS-CoV-2.

Furthermore, it is recognised that more general population-level measures to reduce infection rates (eg, travel restrictions) may inhibit the ability of participants to attend study visits. Necessary healthcare responses at sites to the pandemic (eg, additional infection control measures) may also inhibit the ability of a clinical site to effectively and properly conduct the study. Study visit attendance for dosing and for clinical assessments of treatment response are critical for the scientific value of the study.

Therefore, investigators should not enrol participants unless they have reasonable confidence that throughout the duration of the study:

- Participants will be able to attend study visits, whilst avoiding contact with concentrations of COVID-19 patients (eg, hospital entrances used by such patients); and
- The site will be able to conduct the study effectively and safely, considering relevant national and local factors.

The primary endpoint will be analyzed using a repeated measures mixed effect model which, in the event of missing data, uses all data that are available.

AstraZeneca will routinely conduct risk-based enrolment assessments on a country and site level during the pandemic phase of COVID-19, and study monitoring will include:

- AEs associated with new onset SARS-CoV-2 infection
- Participants withdrawn due to COVID-19 illness
- Missed visits due to COVID-19 related issues
- Other missing data.

It is accepted due to age, disease under study and common comorbidities the target population has risk-factors for severe COVID-19 illness. The ability to exclude the most at-risk patients whilst maintaining the target population and the relevance of the study is necessarily limited.

COPD may be a risk-factor for severe COVID-19 illness, and the following participants will not be included in the study (see Exclusion Criteria 1 and 2, Section 5.2):

1 Participants with active COVID-19 infection at screening.

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

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

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

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

Because the screening/run-in period is at least 4 weeks, participants will be tested for active SARS CoV-2 infection using a nucleic acid test targeting SARS-CoV-2 at both screening visits (see SoA [Table 2]), and those with a positive result at either screening visit will become screen failures. This test may be performed either at a local laboratory or at the central laboratory.

Participants suspected of having contracted COVID-19 should be managed according to local and national guidelines to prevent spread of COVID-19 infection to staff and patients. These participants, as well as any who test positive for SARS-CoV-2, should not be automatically discontinued from investigational product or be withdrawn from the study. Investigators should refer to Section 7 when considering participant discontinuation or withdrawal decisions. Sites will be required to provide documentation of a COVID-19 screening and mitigation plan that describes how and where participants would be tested if they are suspected to have SARS-CoV-2 infection. The plans should also describe mitigation activities designed to protect site staff and others at the site, including other participants and patients. Appendix J contains an example screening questionnaire that may be used prior to each visit to identify participants with symptoms of, or recent risk factors for, SARS-CoV-2 infection.

Infection control measures should be followed in accordance with local and national guidelines including, but not limited to, staff screening and use of personal protective equipment.

4.1.1.1 Vaccination Against COVID-19

There is no clinical data available to assess the interaction (if any) of MEDI3506 with any COVID-19 vaccine.

The sponsor accepts that vaccination against COVID-19, when and where it is available and participants are eligible according to applicable guidelines, is in the participant's best interest.

Consequently, vaccination during the study is, in general, permitted and any delays in vaccination due to study participation should be minimized.

To help ensure the interpretability of safety data, receipt of COVID-19 vaccine (either first or subsequent dose) is prohibited within 30 days before randomization or within 7 days before or after any dose of IP (Section 6.5.5). Receipt of, at least, the first dose of COVID-19 vaccine more than 30 days before randomization, without significantly delaying enrolment, should be preferred but may not be possible, eg, not locally available at the time, participant not eligible at the time, express participant decision not to be vaccinated. Otherwise, vaccination may be performed at any time outside the prohibited 7-day window before or after any dose of IP. If the (approximate) date of a subsequent dose of COVID-19 vaccination is known, then enrolment of the participant should be timed so that that dose is not within 30 days prior to scheduled randomization. If this date is not known then enrolment into study should not be delayed. If an enrolled participant does (unexpectedly) receive COVID-19 vaccine within 30 days prior to scheduled randomization, the site should contact the AstraZeneca Study Physician for advice on how the situation should be managed.

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

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

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

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

- Pausing recruitment and screening of new participants
- If, for reasons related to the COVID-19 pandemic, a participant is not able to attend their scheduled visit within the ± 3 day visit window, they can have their visit rescheduled within 14 days of the original scheduled visit; however, visits that cannot be rescheduled within a 14 day window must be skipped and participants should continue at the next scheduled visit.
- During the COVID-19 pandemic, on-site visits may be replaced by a telemedicine visit. Having a telemedicine visit with the participants will allow collection of data for AEs, concomitant medications, and adherence to the eDiary and ePRO measures to be reported and documented. The term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- Performance of clinic spirometry at an alternative location where the participant may perform spirometry manoeuvres under supervision, eg conducted at participant's home by qualified site staff.

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

4.2 Scientific Rationale for Study Design

Chronic obstructive pulmonary disease is a heterogeneous disease (Segal and Martinez 2018) and as such any proposed treatment should be targeted at the participants within that diagnosis most likely to respond, and with the greatest unmet burden of disease. Chronic obstructive pulmonary disease is characterized by airflow limitation (post-BD $FEV_1/FVC < 0.70$) that is not fully reversible, usually progressive and associated with an enhanced chronic inflammatory response in the lung. The Evaluation of COPD Longitudinally to Identify Surrogate Endpoints (ECLIPSE) observational study of 2163 participants with moderate-to-severe COPD found a mean rate of decline of FEV_1 of 33 mL/year over 3 years, with higher rates of FEV_1 decline in the presence of current smoking, emphysema, and BD reversibility (Vestbo et al 2011). Research on the impact of chronic bronchitis in COPD patients on mortality and FEV_1 decline in a population-based cohort, showed that COPD participants with chronic bronchitis (n = 172) had a greater FEV_1 decline (-38 mL/year, 95% CI -61.7 to -14.6; p = 0.024) compared with COPD participants without chronic bronchitis, and also a higher risk of respiratory mortality (hazard ratio 2.16, 95% CI 1.12 to 4.17; p = 0.002) and increased risk of acute exacerbations (objective response 4.0, 95% CI 2.7 to 5.9; p < 0.001) (Lahousse et al 2017). However, emerging evidence (Dunican et al 2021; Kim et al 2021) demonstrates mucus hypersecretion at all stages of COPD, evident on CT imaging alongside even very extensive emphysema. This accumulation of mucus in the small airways can occur in the absence of significant symptoms (Hogg et al 2007), likely as a result

of the lack of cough receptors in the peripheral airways (Burgel and Nadel 2008). Patients with recurrent exacerbations have higher sputum inflammatory markers (Bhowmik et al 2000) which suggests that underlying inflammation may lead to disease progression, but yet may still contribute to the ongoing inflammation associated with disease progression (Anzueto 2010; Crooks et al 2000).

Patients with COPD and mucus hypersecretion therefore present a high unmet need. Current therapy for these patients consists of dual (ICS + LABA or LABA + LAMA) or triple therapies (ICS + LABA + LAMA), with add-on in the event of increased exacerbation history of such treatments as PDE4 inhibitors, and chronic macrolide (such as azithromycin) treatment. These add-on treatments, however, have issues associated with individual tolerability and antibiotic resistance which have hampered their use.

As discussed in Section 2.2, MEDI3506 mode of action is hypothesized to impact airway inflammation, mucus and cough symptoms, and lung function endpoints in COPD, and through modification of these factors, reduce frequency and severity of exacerbations.

This study tests the hypothesis that MEDI3506 will improve lung function in participants with COPD and chronic bronchitis, using FEV_1 as the primary outcome measure. The study uses secondary outcomes to gather evidence to support the mode of action of MEDI3506, concentrating on lung physiology, mucus, cough, and ePROs related to symptoms and disease impact. CCI [redacted]

There will be one sub-study in this trial:

CCI [redacted]

4.2.1 Rationale for Study Population

Chronic bronchitis by physician assessment of participant disease history (presence of cough and phlegm on most days for ≥ 3 months/year for ≥ 2 years) and BCSS average score ≥ 2 in cough and sputum domains over the 4-week run-in period allow not only the standard definition of chronic bronchitis history to be used to define participants who could benefit, but also to increase the chances of seeing a measurable effect size in BCSS and other symptom related measures. This BCSS inclusion criterion helps to identify those patients with symptomatic mucus hypersecretion most likely to respond to MEDI3506 due to its mechanism of action. However, the ability to score severity of emphysema on CT scan will also allow for

analysis of subpopulations of patients with COPD based upon extent of emphysema to further examine the relationship between emphysema and response to MEDI3506.

During the ongoing COVID-19 pandemic, as a result of changed patient behaviour, there has been a significant reduction in exacerbation frequency compared with previous years. Data from the UK suggested a 50% reduction in exacerbation related-hospital admissions compared with pre-pandemic (Tan et al 2020; Alsallakh et al 2021), and a 39% reduction in primary care consultations related to COPD. This picture is replicated in other countries. Leaving the requirement for at least one moderate or severe exacerbation in the previous 12 months unchanged would lead to the exclusion of patients who in previous years would have been included.

In this study, participants are required to have at least one moderate or severe exacerbation in the previous 24 months, as participants with frequent exacerbations have been shown to have an increased symptom burden and likelihood of subsequent exacerbations (Hurst et al 2010), and a history of exacerbation also results in poor outcomes irrespective of ICS use and for exacerbation history of ≥ 1 moderate exacerbation (Carmeley et al 2017). Participants should be clinically stable and free from an exacerbation of COPD for 1 month prior to SV1 and prior to Day 1.

4.2.2 Rationale for Primary Endpoint

The primary endpoint is change from baseline to Week 12 in clinic pre-BD FEV_1.

Forced expiratory volume in 1 second is a validated and clinically important endpoint in COPD studies, and has been used extensively in trials used to support registration of add on therapy to current standard of care (dual/triple therapy) in a similar chronic bronchitis patient population (Martinez et al 2015).

4.2.3 Rationale for Intervention Period Duration

The last dose is administered at Week 24 and the end of treatment is 4 weeks later (Week 28).

Based on available data, the improvement in FEV_1 assumed in the sample size determination (Section 9.2) is expected to be achieved by Week 12. However, improvement in FEV_1 is considered important but not sufficient to meet the unmet medical need in COPD. To enable evaluation of the secondary endpoint of COPDCompEx, the treatment is continued after collection of primary endpoint data, to collect further events. CCI

[redacted]

4.2.4 Participant Input into Design

The AstraZeneca Patient Partnership Program is an internal working group that enables study participant feedback on clinical trial study designs. During study development, the Patient Partnership Program influenced the following aspects of the study design:

- Provision written into the CSP to rotate injection sites.
- Participant training for the eDiary and spirometry devices used at home will be supported by trouble shooting and technical guidance
- Participants may be provided with a single source study guide providing study rationale and guidance in seeking additional support from sites (does not directly affect the CSP).
- There may be ongoing communications with participants such as newsletters and regular site contact (does not directly affect the CSP).
- Site facilities were explored to support participant focused visits such as out of office or TC visits (does not directly affect the CSP).
- A centralized recruitment program may be used.
- Nasal sampling will not be repeated in participants that are unsuitable for repeat sampling as judged by the Investigator.

In addition, a study coordinator review of the SoA took place in order to ensure the SoA was feasible and realistic, particularly in terms of visit duration. This consultation led to the following alterations to the SoA:

- Provision for allowing informed consent at a separate, stand-alone visit has been included in the CSP.
- Detailed guidance has been included to clarify the order of assessments in Section 8.
- Duration estimates for visits were confirmed.

4.3 Justification for Dose

In this proof-of-concept study, a dose regimen of CCI Q4W SC will be administered for 7 doses. This dose is predicted to have a lower exposure, in terms of $C_{max,ss}$ (approximately 2.4-fold) and AUC (approximately 1.1-fold), compared with the highest dose administered (ie, single dose of CCI IV MEDI3506) in the Phase I clinical study (Study D9180C00001; refer to IB for further details).

Exposures (ie, $C_{max,ss}$ of 1276 µg/mL and $AUC_{0\text{-}4\ weeks}$ of 28012 µg day/mL) achieved at the 26-week no observed adverse effect level of 150 mg/kg in cynomolgus monkeys (refer to the IB for further detail) are approximately 38- to 47-fold higher than predicted at the proposed maximum dose of CCI SC Q4W in this Phase II clinical study.

The optimal serum concentration for MEDI3506 efficacy in COPD is not known. A mouse challenge model suggests a target concentration of 20 µg/mL (refer to the IB for additional details). Analysis of the PK data from the Phase I clinical study of MEDI3506 predicts that CCI SC Q4W will achieve an average steady-state concentration of 21 µg/mL, similar to the target concentration established in the mouse model. In addition, this dose is predicted to achieve > 90% suppression of IL-33 in the sputum based on the theoretical PK/PD model. If replicated in humans with COPD, CCI SC Q4W is anticipated to achieve near-maximum efficacy based on the mouse and PK/PD models.

4.4 End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SoA (Table 3) for the last participant in the study globally.

4.4.1 Study Stopping Criteria

Discontinuation of specific sites or of the study as a whole are handled in accordance with Appendix A 9.

The study may be put on hold pending a full safety data review, if any of the following criteria are met:

- Five or more (in different participants) reports of new onset symptomatic heart failure confirmed by echocardiography [1]
- Four or more (in different participants) reports of Grade 5 severity infection (excluding COVID-19 infection), not associated with a COPD exacerbation [1]
- Two or more (in different participants) reports of new onset non-infective colitis, confirmed histopathologically
- Two or more cases of ≥ Grade 4 severity hypersensitivity reactions (eg, anaphylaxis), except where a specific alternative causative allergen is identified [1]
- Ten or more (in different participants) other clinically significant (≥ Grade 4 severity) AEs (excluding those described in any of the preceding criteria) in the same system organ class (excluding COVID-19 infection and COPD exacerbations) that preclude continuing dosing of the participant, unless obviously not related to the IP (eg, motor vehicle accident) [1]
- Participant enrolment is unsatisfactory
- Non-compliance that might significantly jeopardize the validity or integrity of the trial, or safety of the participant(s)
- Sponsor decision to terminate development.

[1] Except if the DSMB confirm that there is no evident significant adverse imbalance between treatment groups and hence this criterion need not apply.

If the sponsor determines that temporary suspension or termination of the study is required, the sponsor will discuss the reasons for taking such action with all participating investigators (or heads of the medical institutions, where applicable). When feasible, the sponsor will provide advance notice to all participating investigators (or heads of the medical institutions, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, the sponsor will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. The sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study. The investigator shall also promptly inform the participant of the study suspension/termination and should assure appropriate participant therapy and/or follow-up.

5 STUDY POPULATION

Each participant must meet all the inclusion criteria and none of the exclusion criteria (excluding sub-study specific criteria) for this study in order to be assigned/randomized to the study intervention. Under no circumstances can there be exceptions to this rule. Participants who do not meet the eligibility requirements are screen failures (refer to Section 5.4). Participants who provide informed consent to participate in the CT sub-study but are subsequently found not to meet all of the inclusion criteria and/or meet any of the exclusion criteria, applicable to the sub-study, should not participate further in the sub-study but should continue to participate in the main study so long as they are eligible as described above.

In this CSP, “enrolled” participants are defined as those who sign the ICF. “Randomized” participants are defined as those who undergo randomization within the RTSM system.

Prospective approval of CSP deviations to eligibility criteria, also known as CSP waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

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

Age:

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

PPD

Type of Participant and Disease Characteristics:

2 Participants who are current or ex-smokers with a tobacco history of ≥ 10 pack-years. Pack-years are calculated as average number of cigarettes per day × number of years / 20. For example, 1 pack-year = 20 cigarettes smoked per day for 1 year or 10 cigarettes per day for 2 years.

3 This inclusion criterion has been removed.

4 Participants who have a documented history of COPD for at least 1 year. A verbal history of symptoms consistent with COPD from the participant is not sufficient. Acceptable documentation includes

- Clinic visit (primary or specialist HCP) notes or emergency room/hospital records listing COPD as a current diagnosis
- Verbal discussion confirming the diagnosis of COPD between the investigator and physician who has access to the participant's medical record. The investigator is required to clearly document this conversation in participant's source document.

5 Participants who have a post-BD $FEV_1/FVC < 0.70$ and a post-BD $FEV_1 > 20\%$ and $< 80\%$ predicted normal value at screening. Centralized spirometry will be used for this criteria assessment.

6 Participants who have a physician confirmed history of chronic bronchitis as defined as presence of cough and sputum on most days for ≥ 3 months/year in at least the 2 year period immediately prior to SV1 (screening). Assessment based on a verbal history consistent with chronic bronchitis is sufficient.

7 Participants who have an average RCSS score of ≥ 2 in cough and ≥ 2 in sputum domains assessed over the 14 days preceding SV3.

8 Participants who have a documented stable regimen of dual therapy or triple therapy for ≥ 3 months prior to enrolment; there should have been no change in treatment after the previous exacerbation prior to entering into the study. Where dual therapy consists of ICS + LABA or LABA + LAMA, and triple therapy consists of ICS + LABA + LAMA. Both dual and triple therapy may be in the form of separate inhalers of fixed dose combination inhalers but may not be in nebulized form. However, all inhalers must be locally approved for the maintenance treatment of COPD. See Section 6.5.1. Acceptable documentation includes:

- Recent, active medication list as per HCP note
- Filled prescriptions based on a pharmacy record
- Another acceptable medical record as per local clinical practice
- Verbal discussion confirming treatment regimen between investigator and HCPs who have access to participant's medical record. The investigator is required to clearly document this conversation in participant's source document.

PPD

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

- Clinic visit (primary or specialist HCP) notes or emergency room/hospital records providing evidence of ≥ 1 moderate or severe AECOPD in the previous 24 months prior to enrolment.
- Documented prescription of systemic corticosteroids of at least 3 days duration (or 1 injection of depot formulation) and/or antibiotics for treatment of exacerbation
- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant was hospitalized or treated with systemic corticosteroids for a COPD exacerbation.
- Verbal confirmation from the patient that they have self-administered rescue medication for an acute exacerbation, characterised as above, in the previous 24 months, despite confirmation of compliance with usual inhaled medication. This needs to be clearly documented in the participant's source document by the investigator.

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

11 Participants who are at least 70% compliant with the eDiary and home spirometry during the 14 days preceding SV3 based on the eDiary.

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

Weight:

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

Sex/Reproduction:

14 Female participants of childbearing potential, must have negative pregnancy tests at screening SV1 (serum pregnancy test), and then subsequently at SV2 (urine pregnancy test, only if a CT scan is performed) and pre-dose of study intervention at SV3 (Day 1; urine pregnancy test).

15 Female participants of childbearing potential who are sexually active with a male partner must agree to use a highly effective method of contraception from screening until the end of the follow-up period at SV14 of the study. See Appendix F for definitions of childbearing potential and highly effective methods of contraception. In countries where spermicide is available, it is strongly recommended for the male partner of a female participant of childbearing potential to also use male condom plus spermicide throughout

this period.
In countries where spermicide is not available, it is strongly recommended for the male partner of a female participant of childbearing potential to also use male condom throughout this period.
Note there are no contraception requirements for female participants who are not of childbearing potential. However, all female participants should refrain from egg cell donation and breastfeeding throughout the study.

16 In countries where spermicide is available, male participants who are sexually active with a female partner of childbearing potential must agree to use a male condom with spermicide and another highly effective method of contraception during the intervention and follow-up periods from Day 1 through to SV14 of the study.
In countries where spermicide is not available, male participants who are sexually active with a female partner of childbearing potential must agree to use a male condom and another highly effective method of contraception during the intervention and follow-up periods from Day 1 through to SV14 of the study.
See Appendix F for definitions of childbearing potential and highly effective methods of contraception. Male participants should also refrain from biologically fathering a child or donating sperm during the same period.

Informed Consent:

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

Informed Consent (Sub-studies):

18 Provision of signed and dated written informed consent for sub-study enrolment (if applicable).

5.2 Exclusion Criteria

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

Medical Conditions and Diagnostic Assessments

1 Participants with a positive diagnostic nucleic acid test for SARS-CoV-2 at SV1 or SV2. Subjects with mild or asymptomatic disease could be rescreened.

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

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

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

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

3 As judged by the investigator, any evidence of any active medical or psychiatric condition or other reason (at screening [SV1 and SV2] and SV3 [pre-dose]) which in the investigator's opinion makes it undesirable for the participant to participate in the study. This includes but is not limited to:

(a) Diabetes mellitus, except for participants with type 2 diabetes mellitus who are well controlled in the opinion of the investigator.

(b) History of heart failure.

(c) Clinically significant or unstable ischemic heart disease, arrhythmia including atrial fibrillation (except first degree heart block), or cardiomyopathy, including acute coronary syndrome within the last 6 months; or any history of myocardial infarction.

(d) Clinically significant aortic stenosis.

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

(f) Pulmonary arterial hypertension to exclude participants with known history of primary pulmonary arterial hypertension or clinically significant cor pulmonale.

(g) History of an underlying condition that predisposes the participant to infections (eg, history of splenectomy, known primary or secondary immune deficiency syndromes).

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

4 This exclusion criterion has been removed.

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

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

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

(c) A diagnosis of asthma made when the subject was aged ≥ 40 years, confirmed by the investigator to be a misdiagnosis after discussion with and agreement of the AstraZeneca Study Physician.

6 Clinically important pulmonary disease other than COPD (eg, active lung infection, clinically significant bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha-1 anti-trypsin deficiency and primary ciliary dyskinesia) or another diagnosed pulmonary or systemic disease that is associated with elevated peripheral eosinophil counts (eg, allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome, hypereosinophilic syndrome),

radiological findings, and/or laboratory findings suggestive of a respiratory disease other than COPD that is contributing to the participant's respiratory symptoms.

7 Increased pre-BD FEV_1 at randomization visit (SV3) compared to Screening SV1 of ≥ 400 mL or ≥ 25% of SV1 FEV_1.

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

9 Any other clinically relevant abnormal findings on physical examination, laboratory testing including hematology, coagulation, serum chemistry, or urinalysis; or chest CT scan at screening or randomization, which in the opinion of the investigator or medical monitor may compromise the safety of the participant in the study or interfere with evaluation of the study intervention or reduce the participant's ability to participate in the study. Abnormal findings include, but are not limited to:

(a) ALT or AST > 2 × ULN.

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

(c) Evidence of chronic liver disease

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

(i) Systolic BP < 80 mmHg or ≥ 150 mmHg.

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

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

(e) This exclusion criterion has been removed.

(f) Any clinically significant rhythm, conduction, or morphology abnormalities in the 12-lead ECG including but not limited to corrected QT interval (Fridericia) (Vandenberk et al 2016) > 450 ms.

(g) Chest CT scan finding requiring further investigation or repeat CT surveillance before SV14.

10 This exclusion criterion has been removed.

11 A family history of heart failure defined as either of the following: ≥ 2 first degree relatives with clinically significant heart failure, or ≥ 1 first degree relative with heart failure known to be heritable (eg, hypertrophic cardiomyopathy), unless inheritance is excluded by genetic testing.

12 A LVEF < 45% measured by echocardiogram during screening, between the time of signing informed consent and prior to randomization.

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

14 Prior history of/planned: lung pneumonectomy for any reason, or lung volume reduction procedures (including bronchoscopic volume reduction) for COPD. Note: Surgical biopsy, or segmentectomy, or wedge resection, or lobectomy for other diseases would not be excluded.

15 Long term oxygen therapy (a requirement for continuous oxygen therapy > 16 hours per day).

16 Use of any non-invasive positive pressure ventilation device.

17 Current diagnosis of cancer.

18 History of cancer, except if treated with apparent success with curative therapy (response duration of > 5 years).

19 A known history of severe reaction to any medication including biologic agents or human gamma globulin therapy.

20 A helminth parasitic infection diagnosed within 6 months prior to SV1 that has not been treated with, or has failed to respond to, standard of care therapy.

21 History of herpes zoster within 3 months prior to randomization (Day 1).

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

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

24 A positive test for HIV or known to have HIV infection.

25 Evidence of active or untreated latent TB infection (LTBI) as evidenced by

(a) Positive IGRA test and evidence of symptoms suggestive of active TB

(b) Positive IGRA, or repeated indeterminate IGRAs, no evidence of active TB and untreated for latent infection, unable to be treated for, or declines treatment of latent TB infection.

(c) Participants newly diagnosed with LTBI on initial screening could be considered for rescreening if they complete a full course of treatment for latent TB in accordance with recommended treatment guidelines prior to rescreening. In this situation, repeat IGRA test is not required after completion of treatment for LTBI.

(d) Participants with an indeterminate IGRA should undergo repeat test and if still indeterminate may only be enrolled after treatment for latent TB infection.

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

Prior/Concomitant Therapy

27 Participants currently receiving background therapy that is not approved by regulatory authorities in the country of study for COPD are not eligible for the study.

28 History of treatment with cardiotoxic medications (eg, as part of cancer therapy) including thiazolidinediones.

29 Major surgery within 8 weeks prior to screening or planned inpatient surgery or hospitalization during the study period. Elective hospitalizations that cannot be delayed until after the end of the study need to be discussed with the sponsor's medical monitor.

30 Treatment with broad spectrum antibiotic within 4 weeks prior to randomization (Day 1).

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

32 History of allogeneic bone marrow transplant.

33 Treatment with allergy immunotherapy within 90 days prior to SV1.

34 Receiving any of the prohibited concomitant medications as specified in the CSP:

(a) Acute systemic (oral or injectable) corticosteroids within 4 weeks of SV1

(b) Any other immunosuppressive therapy (including methotrexate, cyclosporine or maintenance systemic steroid treatment) within 3 months of randomization.

(c) Immunoglobulin or blood products within 4 weeks of SV1.

(d) Live or attenuated vaccines within 4 weeks of SV1. (Note: Vaccines with adenoviral vectors that are unable to replicate, eg, ChAdOx1, are not considered live or attenuated).

(e) Interferon gamma within 3 months of randomization.

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

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

(h) Any add-on therapy for COPD including theophylline. Chronic macrolide or other antibiotic therapy is allowed provided the participant has been on a stable dose/regimen for ≥ 3 months prior to enrolment and has had at least one COPD exacerbation while on stable therapy.

(i) PDE4 inhibitors (e.g. roflumilast, Daxas®, Daliresp®) commenced within 3 months of SV1. PDE4 inhibitors are allowed provided the participant has been on a stable dose/regimen for ≥ 3 months prior to enrolment and has had at least one COPD exacerbation while on stable therapy.

(j) Vaccination against COVID-19 (either first or subsequent dose) within 30 days prior to randomization.

(k) Any immunotherapy within 3 months of randomization.

(l) Antitussive and mucolytic medications commenced within 4 weeks prior to SV1. Antitussive and mucolytic medications are allowed provided the participant has been on a stable therapy/regimen for greater than 4 weeks.

35 Participation in, or scheduled for, an intensive COPD rehabilitation program at any time during the intervention period (note: participants are permitted to be in the maintenance phase of a rehabilitation program).

Prior/Concurrent Clinical Study Experience

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

Exclusion Criteria for Optional Genetic Sample Only

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

Other Exclusions

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

39 Inability to perform technically acceptable spirometry.

40 Pregnancy or intention to become pregnant during the study, breastfeeding, or unwillingness to use a highly effective method of contraception throughout the study in female participants of childbearing potential.

41 This criterion has been removed.

CCI [redacted]

CCI [redacted]

5.3 Lifestyle Considerations

Participants must abstain from donating blood and plasma from the time of informed consent, and for 16 weeks (5 half-lives) after last dose of study intervention.

5.3.1 Meals and Dietary Restrictions

Participants should avoid eating a large meal for at least 2 hours prior to all scheduled lung function and AO assessments at the site.

5.3.2 Caffeine, Alcohol, and Tobacco

Chronic alcohol or drug abuse within 2 years is restricted prior to SV1 and throughout the conduct of the study.

Current tobacco smokers or prior tobacco smokers, with smoking history ≥ 10 pack-years (1 pack-year = 20 cigarettes smoked per day for 1 year) at SV1 are allowed. Never smokers are not allowed to enter the study. Any change in smoking status in 12 weeks prior to enrolment or intention to change smoking status between enrolment and end of follow-up will result in a screen failure. However, following change in smoking status, they will be eligible for re-screening. Smoking status changes during the course of the study will be captured on the eCRF but the participant will be permitted to continue in the study. See also Section 8.

The use of e-cigarettes (eg, JUUL) is allowed during the course of the study.

5.3.3 Activity

1 Participants should avoid engaging in strenuous exertion for at least 30 minutes prior to all scheduled lung function assessments, AQHA and blood collection at the site.

2 Participants should avoid showers/bathing and any activity that will cause heavy perspiration whilst wearing the cough monitor, as the cough monitor must not come into contact with water.

5.4 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, if there is reason to believe the reason for ineligibility was temporary (eg. exacerbation and/or background medication stability periods). Only one rescreening per participant is allowed in the study, when there is a reasonable expectation that the participant will become eligible for the study. Prior to rescreening, participants must be reconsented. Participants in rescreening retain their previous E-code.

Where individuals are rescreened, the results of echocardiogram and IGRA (TB test) carried out as part of the original screening process can be included as long as they are within the last 3 months and there have been no specific risks of TB infection such as foreign travel to a high

incidence area and no recent cardiac events which may affect the echocardiogram. CCI [redacted] All other tests must be performed as per the schedule of events (Table 2).

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the CSP. Study intervention in this study refers to MEDI3506 and placebo.

6.1 Study Intervention Administered

6.1.1 Study Interventions

Table 6 Study Interventions

ARM Name	MEDI3506 CCI [redacted]	Placebo
Intervention Name	MEDI3506	Placebo
Type	Biologic	Drug
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength(s)	CCI [redacted]	Not applicable
Dosage Level(s)	CCI [redacted]	CCI [redacted]
Route of Administration	CCI [redacted]	CCI [redacted]
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	CCI [redacted]	CCI [redacted]

IMP = Investigational medicinal product; NIMP = Non-investigational medical product; Q4W = Every 4 weeks; SC = Subcutaneous; w/v = Weight per volume.

PPD

6.2 Preparation/Handling/Storage/Accountability of Interventions

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

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

3 MEDI3506 does not contain preservatives and, therefore, any unused portion must be discarded.

The unblinded study intervention manager will select the appropriate kits allocated by the RTSM system to prepare the participant's dose. The unblinded study intervention manager must ensure that only the unblinded team members have access to the areas of the pharmacy where the study intervention is being stored and prepared.

6.2.1 Study Intervention Inspection

Each vial allocated for dose preparation should be inspected. MEDI3506 and placebo are supplied as a clear to opalescent sterile liquids

If there are any defects noted with the study intervention, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section in the IMP manual for further instructions.

6.2.2 Dose Preparation Steps

No incompatibilities between MEDI3506 and plastics (ie, polypropylene and polycarbonate syringes) have been observed.

MEDI3506 and placebo do not contain preservatives and any unused portion must be discarded. Preparation of study intervention is to be performed aseptically. Total in use storage time from needle puncture of the study intervention vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2 °C to 8 °C (36 °F to 46 °F). If storage time exceeds these limits, a new dose must be prepared from new vials assigned by the RTSM system.

A vial should be used only 1 time to prepare a single dose.

To prepare the participant's dose, the unblinded study intervention manager will select study intervention for administration according to the kit identification numbers assigned. A

summary of the study intervention volumes required and syringes to prepare for SC dose administration in each study intervention group is provided (Table 7).

Table 7 Study Intervention Dose Preparation

Contents of vial(s)	Number of kits	Volume required	Syringes to prepare	Size of syringe	Total volume of study intervention
CCI **MEDI3506 intervention group**					
MEDI3506	CCI				
Placebo intervention group					
Placebo	CCI				

The dose preparation steps are as follows:

1 Prepare the assigned MEDI3506 and/or placebo vials for the particular study intervention group as per Table 7.
2 Withdraw the required volume of MEDI3506 or placebo from each vial using a separate, appropriately sized syringe and a separate 18 to 20-gauge 1 to 1.5 inch needle, respectively.

CCI

6.2.2.1 Study Intervention Administration

The first day of dosing is considered SV5 (Day 1).

Female participants of childbearing potential, must have a negative urine pregnancy test prior to receiving each dose of study intervention.

MEDI3506 and placebo are CCI The syringes should be kept out of sight of all blinded persons, including the participant, to maintain the blind. Study intervention will be administered CCI by unblinded site personnel CCI to the abdomen, back of the arms, or thigh. CCI CCI apart in the same anatomical region. CCI administering the dose will wipe the skin surface of the administration sites with alcohol and allow the skin surface to air dry. The skin will be pinched to isolate the SC tissue from the muscle. The needle will be fully inserted at a 45 degree angle into the SC tissue. The study intervention will be slowly injected (at least 5 seconds duration is recommended). The area should not be massaged after injection.

It is advised that the site of injection be rotated so that the participant receives study intervention injections in different anatomical regions from one visit to the next. In cases when rotation of the injection site is not feasible and/or the participant prefers not to rotate injection sites, the reason for not rotating the injection site should be documented in the source documents.

Each injection site must be documented on the eCRF and in the source documents at each study intervention visit.

6.2.2.2 Monitoring Dose Administration

After the administration of study intervention, vital signs will be assessed according to the SoA (Section 1.3), and SC injection sites will be assessed for any reactions as detailed in Section 8.2.3.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis (Appendix I).

6.2.3 Accountability

The site's designated unblinded study intervention manager is required to maintain accurate study intervention accountability records. Upon completion of the study, copies of study intervention accountability records will be returned to AstraZeneca. All unused study intervention and vials will be disposed of following site procedures and upon authorization by AstraZeneca, or will be returned to an AstraZeneca-authorized depot if a site is unable to dispose of unused study intervention. The outer carton should be kept onsite to assist with kit assignment checks, if permitted by site procedures.

6.3 Measures to Minimise Bias: Randomization and Blinding

6.3.1 Methods for Assigning Study Intervention Groups

All participants will be centrally assigned to randomised study intervention using an RTSM system and will be stratified by baseline eosinophil count (< 300 cells/µL, ≥ 300 cells/µL) and background medication usage (ICS or no ICS).

Before each site is initiated, the login information and directions for the RTSM system will be provided.

Study intervention will be dispensed at the study visits summarized in SoA (Section 1.3).

The RTSM system will provide to the investigator(s) or pharmacists the kit identification numbers to be allocated.

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

6.3.2 Methods to Ensure Blinding

Participants will be randomly assigned in a 1:1 ratio to receive study intervention (MEDI3506 CCI or placebo). Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study.

Since MEDI3506 and placebo are not identical, study intervention will be handled by an unblinded study intervention manager at the site and will be administered by an unblinded study team member who will not be involved in the management of study participants. An independent study intervention monitor will also be unblinded to perform study intervention accountability. In the event that the study intervention allocation for a participant becomes known to the investigator or other study staff involved in the management of study participants, AstraZeneca must be notified *immediately*. If the study intervention allocation for a participant needs to be known to treat an individual participant for an AE (Section 6.3.3), the investigator must notify AstraZeneca *immediately*. The site will maintain a written plan detailing which staff members are blinded/unblinded and the process of study intervention preparation and administration used to maintain the blind.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

To facilitate the in-stream analysis of PK and ADA samples, the randomisation schedule may be provided to limited personnel who have responsibility for analysing the samples. These unblinded sample analysts will not have any other involvement with the conduct of the study.

MEDI3506 could reduce eosinophil counts in blood over time. As a precaution, eosinophil, basophil, and monocyte data from the hematology laboratory tests will not be communicated to blinded sponsor or site personnel during the intervention and follow-up periods. These data do not require blinding at baseline (SV1 to SV3 pre-dose).

6.3.3 Methods for Unblinding

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the study intervention randomization. The investigator documents and reports the action to AstraZeneca, without revealing the study intervention given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to study intervention and that potentially require expedited

reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The RTSM system will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the study intervention given to participant to the AstraZeneca staff.

6.3.3.1 Unblinding for Analysis Purposes

An interim analysis may be included in this study prior to the Primary Analysis. Should an interim be conducted, the purpose will 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 since the interim analysis would be for administrative purpose only.

An interim analysis will require unblinding of a group of sponsor staff or designated representatives including those with clinical, medical, statistical, and programming expertise, who will form a firewalled unblinded review committee for administrative purposes. The unblinded review committee will be responsible for reviewing the interim results and will ensure that the review is performed in a way that maintains the integrity of the trial, and in accordance with the interim analysis unblinding plan, which will be prepared prior to the interim analysis. Sponsor staff and designated sponsor representatives who conduct the interim analysis will take no further part in any study activities after they are unblinded. They will not reveal the interim analysis results or study intervention codes to any of the study team member (sponsor staff or representative) who will remain blinded and continue to be involved in the study's conduct until completion as originally planned. In addition, interim analysis results will not be shared with investigators or participants. The scope and additional details on interim analyses are provided in Section 9.5.

There are 3 planned analyses for this study as described in Section 9.5. Personnel from AstraZeneca or its representatives directly associated with the conduct of this study will remain blinded until the completion of the Primary Analysis. Personnel from the study sites, and the study participants, will remain blinded until the completion of the Final Analysis.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from an unblinded Product Administrator, who is appropriately trained. The date and time of the dose administered (first injection) in the clinic will be recorded in the source documents and recorded in the eCRF.

6.5 Concomitant Therapy

The investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

Investigators may prescribe concomitant medications or treatments that are:

- not prohibited (see Section 6.5.5),
- neither compromise participant safety not affect study data, as judged by the investigator; and
- deemed necessary to provide adequate supportive care.

Specifically, participants should receive full supportive care during the study, including intermittent treatment with antibiotics, antiemetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants are recommended to be vaccinated against influenza and pneumonia according to local schedule. Vaccination is permitted during the study but not within ±7 days of dosing.

6.5.1 Required Maintenance Therapy for COPD

All participants are required to be treated with stable doses of maintenance dual inhaled (ICS + LABA or LABA + LAMA) or triple inhaled therapy (ICS + LABA + LAMA) for COPD for at least 3 months prior to enrolment (SV1). Both dual and triple therapy may be in the form of separate inhalers or fixed dose combination inhalers but may not be in nebulized form. However, all inhalers must be locally approved for the maintenance treatment of COPD. Maintenance treatment should remain unchanged throughout the duration of the study (except for treatment of COPD exacerbations, see Section 6.5.4). If a change in COPD maintenance treatment is required, it must be discussed with the medical monitor.

Note: The Spiriva Respimat device is considered to be an inhaler.

6.5.2 CCI

CCI [redacted]

6.5.3 Medication Withhold Periods

The following medication withhold periods should be observed prior to scheduled spirometry and AO at site:

- SABA and SAMA for at least 6 hours prior.
- Twice daily LABA or LAMA-containing therapies for at least 12 hours prior.
- Once daily LABA or LAMA-containing therapies for at least 24 hours prior.

If any of the restrictions are not met and the spirometry session cannot be sufficiently delayed on the day, it should be rescheduled within the allowed visit window.

Spirometry assessments will also be performed at home daily (except on days when the participant is attending at site visits). Instructions regarding the participant's medication and home spirometry sequence are described in Section 8.1.3

6.5.4 Treatment of Exacerbations of COPD

In general exacerbations of COPD should be treated according to the judgment of the treating physician in line with local guidelines.

Both systemic corticosteroids and antibiotics used to treat a COPD exacerbation should not be used for more than 14 days. If treatment duration is expected to exceed 14 days, the medical monitor must be contacted. An increased dose of ICS may be used alongside OCS, however it should be returned to usual maintenance dose at resolution of the exacerbation.

Medications may be administered by nebulizer if required during the course of an exacerbations. Scheduled use of SABA/SAMA and oxygen supplementation is permitted during the course of an exacerbation.

6.5.5 Restricted and Prohibited Medications

The following medications are restricted from SV1 to the end of the follow-up period, unless clinically indicated, as determined by a physician:

- Acute systemic (oral or injectable) corticosteroids within 4 weeks of SV1 until the end of the follow-up period, except for treatment of acute exacerbations of COPD during the course of the study.

- Macrolide therapy except for:
  - Chronic macrolide or other antibiotic therapy is allowed provided the participant has been on a stable dose/regimen for ≥ 3 months prior to enrolment and has had at least one COPD exacerbation while on stable therapy OR
  - Acute use of macrolides to treat infections and exacerbations of COPD is permitted.
  - Participants who received ≥ 6 months of macrolide treatment in the previous year must have a hearing assessment per local standard practice 3 months prior to enrolment or during the screening period; these participants must be interviewed for potential hearing issues/tinnitus at enrolment and any reported issues will be recorded as part of medical history.
- Long term oxygen therapy (continuous oxygen therapy for > 16 hours per day).

CCI

[redacted]

The following medications are prohibited (for the time periods stated):

- Any immunosuppressive therapy (other than corticosteroids) within 3 months of randomization until the end of the follow-up period.
- Any immunotherapy within 3 months of randomization
- Interferon gamma within 3 months of randomization until the end of the follow-up period.
- Investigational products other than MEDI3506 within 4 months or 5 half-lives (whichever is longer) prior to randomization until the end of the follow-up period.
- Marketed biologics within 4 months or 5 half-lives (whichever is longer) prior to randomization until the end of the follow-up period.
- Immunoglobulin or blood products within 4 weeks of SV1 until the end of the follow-up period.
- Live or attenuated vaccines within 4 weeks of SV1 until the end of the follow-up period (Note: Vaccines with adenoviral vectors that are unable to replicate, eg, ChAdOx1, are not considered live or attenuated).
- Vaccination against COVID-19 (either first or subsequent dose) within 30 days before randomization or within 7 days before or after any dose of IP
- Antitussives medications commenced within 4 weeks prior to SV1 until the end of the follow-up period
- Mucolytic medications (eg. carbocysteine) commenced within 4 weeks prior to SV1 until the end of the follow-up period
- Roflumilast (Daxas®, Daliresp®) and other PDE4 inhibitors commenced within 3 months of randomization until the end of the follow-up period.

PPD

Other than the permitted medications, use of concomitant medications or therapies from screening through to the early discontinuation visit/end of study is discouraged. Medications or therapies that are not prohibited and neither compromise participant safety nor affect study data, as judged by the investigator, will be permitted.

6.5.6 COVID-19 Vaccination

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

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

Details for how this information should be entered into the eCRF will be provided in separate guidelines.

Any AEs suspected due to the vaccination should be captured in the AE form along with the causality assessment if related to COVID-19 vaccine.

6.6 Dose Modification

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

The PI may determine it necessary on medical grounds for a participant to permanently discontinue (definitive discontinuation) study intervention. Note that discontinuation from study intervention is NOT the same thing as withdrawal from the study.

If study intervention is permanently discontinued, the participant will remain in the study and attend all remaining intervention period and follow-up period visits.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

An individual participant will not receive any further study intervention if any of the following occur in the participant in question:

1 Withdrawal of consent to further treatment with study intervention.

2 Lost to follow-up.

3 Any anaphylactic reaction to study intervention requiring epinephrine administration.

4 Any treatment-emergent AE that is Grade ≥ 4 in severity (see Appendix B).

5 Any treatment-emergent SAE that is in the cardiac disorders system organ class, except atrial arrhythmias.

6 Confirmed diagnosis of new onset of heart failure during the study (except for transient heart failure secondary to atrial arrhythmia). For a participant with suspected new onset of heart failure, the participant should not be administered study intervention unless and until the diagnosis is refuted. Study intervention should also be temporarily withheld during any episode of transient heart failure secondary to atrial arrhythmia.

7 Any other AE that, in the opinion of the investigator or the sponsor, warrants discontinuation of further dosing of study intervention.

8 Pregnancy.

9 Following randomization, the participant meets ≥ 1 of the exclusion criteria or fails to meet all of the inclusion criteria for study participation.

10 Any AECOPD with duration > 14 days.

11 The participant misses 2 consecutive doses.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an E/D should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

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

- The following actions must be taken if a participant fails to return to the clinic for a required study visit:
- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A 9.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Clinical study protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Efficacy Assessments

8.1.1 Clinic Spirometry

8.1.1.1 General Requirements

All spirometry is performed pre-dose.

Lung function (FEV_1 and FVC) will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the investigator or authorized delegate according to ATS/ERS guidelines (Miller et al 2005).

The vendor providing central spirometry is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the site personnel who will be performing the testing are properly certified. Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) will be detailed in a separate spirometry procedures manual and in the monitoring plan. Participants who exhibit unexpectedly high variability of FEV_1 will be evaluated by the investigator for etiology of variability, necessary follow-up actions, and assessment of continued participant eligibility. The investigator will discuss unexpectedly high variability with the AstraZeneca Study Physician.

Participants should observe the relevant medication withhold periods and other restrictions beforehand (see Section 5.3 and Section 6.5.3). If any of the restrictions are not met and the session cannot be sufficiently delayed on the day, the site visit and dosing should be rescheduled within the allowed visit window. All lung function measurements should take place prior to dosing, if dosing is also scheduled at the same visit.

Usual infection control measures should be followed including use of filters, per the instructions of the central vendor. Any additional infection control measures in accordance with COVID-19 related local and national guidelines should also be followed.

Time of day for scheduled site visit spirometry

Spirometry testing should be performed at specified visits according to the SoA (Section 1.3). Spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM during the screening period and at the randomization visit (SV3).

All post-randomization spirometry assessments should be performed within ± 1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Detailed procedure for performing spirometry will be described in an instruction manual. Details regarding assessment of the quality of spirometry and the Best Test Review process will also be detailed in the manual and Monitoring Plan.

Spirometry references

The Global Lung Function Initiative equations will be used to determine the PNV and are pre-programmed into the spirometer (Quanjer et al 2012).

Forced expiratory volume in 1 second expressed as percent of the PNV, will be calculated as follows:

$FEV_1\%\ of\ PNV = (FEV_1\ measured/FEV_1PNV) \times 100$

8.1.1.2 Post-BD Spirometry

Post-BD spirometry will be performed at specified visits as detailed in the SoA (Section 1.3).

Endpoint maximal BD will be induced using albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) with or without a spacer device up to a maximum of 4 inhalations within 30 minutes ± 15 minutes of the final pre-BD spirometry measurement. Post-BD spirometry will be performed 15 to 30 minutes later.

Order of administration for the COPD maintenance medication and study intervention relative to the scheduled pre- and post-BD spirometry

The participant's usual COPD morning maintenance therapy must not be given until spirometry are complete in order to maintain the integrity of planned efficacy analyses around lung function improvement. Study intervention dosing should also be withheld until pre-BD/post-BD spirometry is complete.

Record keeping

A signed and dated copy of the pre- and post-BD printout must be kept at study centre for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, visit number. If a printout cannot be printed, the mean value of the measurements will be recorded in the participant's charts.

8.1.2 Airwave Oscillometry

Airwave oscillometry will be performed at specified visits as detailed in the SoA (Section 1.3), using the endpoints of R5-R20, R5, R20, and AX. Airwave oscillometry is a non-invasive lung function test included in this study, which will be assessed using an AO device. It is assessed during quiet, tidal breathing with no participant effort required, by superimposing a multi-frequency oscillation onto the participant's natural breathing, to

evaluate study intervention effect on small airway function. A centralized vendor will provide the equipment for testing.

A calibrated system will be used for measurements. Detailed procedures for equipment calibration, performance of measures, recording and analyzing AO data will be described in a separate manual provided to each site. Details regarding assessment of the quality of the AO process will also be detailed in the manual.

- All AO function measurements should take place prior to dosing, if dosing is also scheduled at the same visit, and prior to spirometry.
- Participants should observe the medication withhold periods and lifestyle considerations stated in Section 6.5.3 and Section 5.3, respectively.

Note: If any of the above restriction are not met, the AO assessment should be rescheduled within the allowed visit window and should be conducted prior to spirometry.

8.1.3 Home Spirometry and eDiary

During the intervention period, participants will be required to monitor lung function at home using an at-home spirometry device for daily recording of FEV_1 and PEF. This will be done once daily in the morning, with the same time window recommendation as the clinic spirometry; however, the time window is not compulsory (ie, all data will be used for analyses). Participants will be instructed to perform all home spirometry assessments before use of their usual standard-of-care inhaled medication.
Further details will be provided in a separate instruction manual provided to each site.

Participants will be trained on at-home use of the eDiary at SV1. The site staff will set assessment reminder alarms on the device (morning and evening). Training will emphasize the importance of completing the eDiary assessments as scheduled to capture the participant's experience and meet the objectives of the study.

The investigator/authorized delegate will check participant's adherence to the eDiary assessment schedule and also emphasize the importance of transmitting data daily as is necessary, to minimize missing data, and at each study visit.

Every morning participants will perform home spirometry and use the eDiary answer the following questions / questionnaires:

- Major COPD symptoms (dyspnea, sputum volume, and sputum color, see Appendix G)
  - Participant-reported worsening of 1 or more major COPD symptoms will trigger assessment of minor COPD symptoms (sore throat, cold, fever without other cause, cough, and wheeze).

CCI [redacted]

- Nighttime awakening due to respiratory symptoms
- Maintenance medication adherence (not considering reliever usage).

Every evening participants will use the eDiary to answer the following questions / questionnaires:

- BCSS individual symptoms scores (cough, sputum, breathlessness, see Section 8.1.8.3)

CCI [redacted]

- The ER-S:COPD (see Section 8.1.8.1)
- Cough VAS (see Section 8.1.8.2)

The eDiary will generate an alert to the participant and the investigational site if any of the following criteria are met:

- Worsening of 1 major COPD symptom and at least 1 other major or minor symptom for 2 consecutive days.
- Fall in PEF by ≥ 30% from baseline for 2 consecutive days

CCI [redacted]

Baseline is defined as the average of 14 days prior to first dose of investigational product.

This alert should trigger a contact between the participant and the investigational site. Alerts will only be received by site when eDiary uploads/syncs, subject to connection availability, therefore participants may initiate contact with the investigator for assessment of possible AECOPD regardless of any prompts from the site, or the eDiary and spirometry.

The investigator then makes the decision whether or not to initiate (or escalate, as appropriate) treatment for a COPD exacerbation. The investigator site is responsible for documenting the action taken for every alert, in the source notes and relevant eCRF modules, regardless who initiates contact (site or participant).

8.1.4 Objective Cough Monitoring

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 (Section 1.3). Set up of the cough monitors should be performed as the final assessment at each visit.

The sites will receive training to ensure the ACM is correctly fitted and activated by site staff, and the site staff will be given instructions to provide to the participants on how the ACM should be worn during the 24 hour period, to ensure data are recorded correctly. Advice

includes avoiding showers/bathing and any activity that will cause heavy perspiration whilst wearing the cough monitor, as the cough monitor must not come into contact with water (see Section 5.3.3).

The digitally recorded data recorded on the ACM will be sent to Vitalograph who will undertake cough counting for all participants using a standardized process. Details on the process to follow will be provided to the sites as part of the ACM training.

Detailed procedures for set up of device, recording and analyzing objective cough data will be described in a separate manual provided to each site. Details regarding assessment of the quality of objective cough monitoring undertaken by the Vendor will also be detailed in the manual.

8.1.5 COPDCompEx

The COPDCompEx is a composite endpoint for exacerbations in COPD. The COPDCompEx combines exacerbations with events defined from participant e-Diaries and PEF. The definitions for both types of exacerbation are as follows:

- COPDCompEx defined exacerbations: episodes leading to one or more of the following: hospitalization, emergency room visit, treatment with OCS, or treatment with antibiotics. Note, this definition is not exactly the same as is used in Section 8.1.6.
- Diary events: defined by threshold and slope criteria using the following diary and home spirometry variables: overall symptom rating, nighttime awakenings due to symptoms, CCI .

More details on the derivation and analysis of this variable will be given in the SAP.

8.1.6 COPD Exacerbations (AECOPD)

An AECOPD will be defined as a change in the subject's usual COPD symptoms that lasts 2 or more days, is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication. The change in symptoms must include at least one major COPD symptom and at least one other major or minor symptom from the list below:

- Major COPD symptoms: dyspnea, sputum volume, and sputum color
- Minor COPD symptoms: cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause.

These symptoms are captured by the eDiary (see Section 8.1.3). If an AECOPD event is not associated with eDiary alert due to COPD symptoms (eg, technical issue with the eDiary), the investigator should interview the participant and evaluate potential worsening and duration of major and minor symptoms.

If symptoms are acute or have progressed rapidly and require treatment less than 2 days from onset of symptoms, the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

If a subject's symptoms and the overall clinical findings support the diagnosis of a COPD exacerbation, but the subject has not experienced a worsening of at least one major COPD symptom and at least one other major or minor symptom (eg, rapid worsening leading to intubation), the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

A clinical assessment of any potential exacerbation during the intervention and follow up periods will occur either at the next scheduled visit or, if necessary, an additional E/A visit prior to the next scheduled visit (see the SoA in Section 1.3).

8.1.6.1 Severity of AECOPD

An AECOPD will be classified as mild, moderate, or severe based on the following criteria.

An AECOPD will be considered severe if it results in:

- An inpatient COPD-related hospitalization (documentation stating that the subject was hospitalized for the COPD exacerbation or a record of the subject being admitted for ≥ 24 hours to an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).
- COPD-related death

An AECOPD that is not considered severe will be considered moderate if it results in:

- Use of systemic corticosteroids and/or antibiotics for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids

Exacerbations that are neither considered moderate or severe will be considered mild.

8.1.6.2 Duration of AECOPD

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

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

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

- Start date of systemic corticosteroids for AECOPD
- Start date of antibiotics for AECOPD

PPD

- Date of hospital admission due to AECOPD

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

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

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

8.1.6.3 COPD Exacerbation eCRF

The investigator should record all pertinent findings and symptoms associated with the exacerbation event and their duration in source documents and in the COPD exacerbation eCRF. In particular, the investigator should also note any changes in medications related to cardiovascular function at any AECOPD event to enable cardiac event evaluation in this eCRF module.

Associated symptoms of COPD are considered as symptoms of disease under study and will not be recorded as AEs unless considered an SAE.

All COPD related SAEs will also be recorded on the SAE eCRF.

8.1.7 CCI

CCI [redacted]

8.1.8 Patient Reported Outcome Questionnaires

Electronic PRO questionnaires will be completed every day at home and at site visits (as specified in the SoA [Section 1.3]) using a hand-held device. Site personnel and participants will be provided training on the use of the device. For home use, the device will be programmed to automatically alert the participants when to fill out the ePROs. In addition, participants will bring their device to study visits, to use for collection of clinic ePROs, which should be completed as the first clinic assessment. The clinic ePROs will be filled out in this order: ER-S:COPD, cough VAS, BCSS, CCI [redacted] SGRQ, CAT, CCI [redacted] and Study Participant Feedback Questionnaire. Detailed procedures for using the device will be described in a separate instruction manual provided to each site.

8.1.8.1 Exacerbations of Chronic Pulmonary Disease Tool– Patient-reported Outcome (EXACT-PRO) and Evaluating Respiratory Symptoms in COPD (E-RS™:COPD)

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

The E-RS™:COPD is an 11-item ePRO developed to evaluate the severity of respiratory symptoms of COPD (Leidy et al 2014a; Leidy et al 2014b). The E-RS™:COPD is a subset of items from the EXACT-PRO. The E-RS™:COPD was designed to be captured as part of the daily EXACT-PRO assessment. 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. The EXACT-PRO will be captured daily each evening in this study via the eDiary.

8.1.8.2 Cough Visual Analogue Scale (Cough VAS)

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 ever" 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.

8.1.8.3 Breathlessness, Cough and Sputum Scale (BCSS©)

The BCSS©, is a 3-item daily diary (Leidy et al 2003) that assesses the severity of the 3 symptoms: breathlessness, sputum, and cough, each on a 5-point scale. Item scores can 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.

8.1.8.4 CCI

CCI [redacted]

CCI

[redacted]

8.1.8.5 St George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item ePRO instrument developed to measure the health status of participants with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into 2 parts: Part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; Part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 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. Based on empirical data and interviews with patients, a change of 4 units is associated with a minimum clinically important difference. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones and Forde 2009). The SGRQ will be completed using eDiary in accordance with the SoA (Section 1.3) and a 4 week recall version will be used.

8.1.8.6 COPD Assessment Test (CAT)

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 will be performed at the baseline visit (SV1) only to enable sub-analyses based on baseline disease activity status via the eDiary, which will be further described in the SAP.

8.1.8.7 CCI

CCI

[redacted]

PPD

CCI [redacted]

8.1.8.8 Study Participant Feedback Questionnaire

This study will include as an option for participants to complete an anonymized questionnaire, 'Study Participant Feedback Questionnaire' for participants to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses will be used by AstraZeneca to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the participant's disease, symptoms, study intervention effect or AEs and therefore would not be study data. The Study Participant Feedback Questionnaire will be captured electronically at time points indicated in the SoA (Section 1.3) and is subject to agreement in the ICF.

8.1.9 Chest CT

Where an inspiratory chest CT scan has been performed within 6 months of informed consent and can be obtained and is adequate for quantitative assessment it shall serve as the baseline scan. Otherwise, a CT scan will be performed, per Table 2, to serve as the baseline scan.

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

- The participant has **not** had an inspiratory chest CT scan within 6 months of informed consent, which can be obtained and is adequate for quantitative assessment, and
- The participant is believed to be eligible, at the time, according to all inclusion and exclusion criteria

CCI [redacted]

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

All CT scans performed (or used) for the purposes of this study should be locally reviewed by a suitably qualified radiologist for clinical findings outside of emphysema and morphometric assessment, to ensure any incidental clinically important findings are identified and referred/treated appropriately (eg, suspected cancer). (This local review may be performed remotely in accordance with local practices.) If a participant is found to have low-risk abnormalities (eg. nodules) that, according to local guidelines, only require surveillance where the first surveillance scan would be required **after** SV14 then that participant may be included

at the discretion of the investigator. Participants that require earlier surveillance scans or more active investigation must **not** be randomized, per Exclusion Criterion 9(g).

New CT scans must be performed in a standardized way:

All new CT scans should be performed post-BD, ie, within 60 minutes of using up to 4 inhalations of albuterol or salbutamol. When these are undertaken at the same visit as spirometry and small airway measurements, CT should be performed after these assessments, so as not to confound the BD withhold periods. If BD is performed as part of the spirometry assessments, this should be repeated if the BD occurred in excess of 60 minutes prior to the CT scan.

A radiology manual, as well as further training by the imaging vendor, will describe both the process of obtaining new scans and how to submit scans (historical and new) to the imaging vendor. An optimized CT protocol will also be provided to the sites that includes all required scan parameters.

Any clinical findings from historical CT should be recorded on the specific imaging eCRF page for SV1. Any findings based on the local assessment of a new CT scan performed during screening/run-in must be recorded in the corresponding eCRF section for SV3.

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

8.1.9.1 CCI

CCI

CCI

CCI

8.1.10 CCI

CCI [redacted]

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Medical, Surgical, and COPD History

Complete medical and surgical history will include history of COVID-19 and COVID-19 vaccination if applicable, prior and current, medical conditions, past or present cardiovascular disorders, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, psychiatric, genitourinary, drug and surgical history, or any other diseases, disorders, or surgical procedures.

The participant's COPD history will also be collected including questions related to the participant's COPD history, duration of COPD, and COPD medications (both past and current).

8.2.2 Physical Examinations, Weight and Height

- Complete and brief physical examinations will be performed by a licensed HCP (eg, physician, physician's assistant, or licensed nurse practitioner). A complete physical examination will include, but will not be limited to, assessment of general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems.
- A brief physical examination will include, at a minimum, assessments of cardiovascular, respiratory, and nervous systems. Each clinically significant abnormal finding will be recorded in the medical history, and each treatment emergent abnormality, including injection site reactions identified by assessing SC injection sites, will be recorded as an AE.
- Physical examinations, weight and height will be recorded at timepoints specified in the SoA (Section 1.3).

8.2.3 Vital Signs

The nominal timing of vital signs is described in the SoA (Section 1.3). The participant should be in a resting supine position for at least 10 minutes prior to the collection of vital signs, as follows:

- Oral or tympanic temperature
- DBP
- SBP
- Heart (pulse) rate
- Respiratory rate

For the first 2 doses of study intervention, participants are to remain at the site for ≥ 2 hours or until stable, whichever is later. In addition, vital signs will be taken before and immediately after administration of study intervention, and at 30, 60, and 120 minutes (± 5 minutes) thereafter or until stable, whichever is later. For the subsequent doses of study intervention, participants are to remain at the site for ≥ 1 hour or until stable, whichever is later. In addition, vital signs will be taken before and immediately after administration of study intervention, and at 30 and 60 minutes (± 5 minutes) thereafter. Following the observation period, participant discharge will be at the discretion of the investigator.

8.2.4 Electrocardiograms

Electrocardiograms will be performed at timelines as specified in the SoA (Section 1.3) and prior to vital signs, and blood sampling. Electrocardiograms will be done as a single measurement.

The nominal timing of ECGs is described in the SoA (Section 1.3). The ECG assessment should be performed before interventions with the participant (eg, spirometry and administration of the COPD related medications and study intervention). The participant should be in a resting supine position for at least 10 minutes prior to the collection of ECGs. 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). The mean value of each parameter from the triplicate will be used as the baseline value. Electrocardiograms taken at all other times will be single assessments.

Electrocardiograms will be recorded with 12-lead digital ECG devices at a speed of 25 mm/second with amplitude recording of 10 mm/mV. Where possible the same make and model ECG device should be used for recording all ECGs for a particular participant. At least 3 full complexes must be recorded. Date and time settings should be checked regularly and following time changes for daylight savings time. Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placements.

Electrocardiogram device software will be used to assess ECG parameters. All ECGs must be reviewed by the PI or a qualified designee before the participant is permitted to leave the clinic. Abnormalities and obvious changes in ECG parameters from baseline will be assessed by the principal investigator for clinical significance.

Electrocardiogram variables will be collected, as follows:

- Heart (pulse) rate
- RR interval
- QRS interval
- PR interval
- QT interval

8.2.5 Echocardiogram

A transthoracic echocardiogram to assess LVEF will be performed and reported locally (see the SoA in Section 1.3).

It should be performed using local guidelines and standards. All echocardiograms must assess left ventricular end-diastolic and end-systolic volumes, and LVEF by 2D examination. An accepted, objective quantitative method must be used to calculate LVEF (eg, the modified biplane Simpson's rule). For each participant, the same quantitative method used to assess LVEF at their first echocardiogram undertaken, during the screening period, must be applied to all subsequent assessments of LVEF.

Routine examination beyond left ventricular end-diastolic and end-systolic volumes, and LVEF is not required unless clinically indicated. However, a standard 2D echocardiogram must be performed in any participant with an abnormal LVEF (< 40%), in order to identify potential causes of depressed left ventricular function.

8.2.6 Clinical Safety Laboratory Assessments

The nominal timing of blood draws is described in the SoA (Section 1.3). A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study. Clinical laboratory safety tests will be performed in a central clinical laboratory with the exception of the SARS-CoV-2 nucleic acid test which may be performed either locally (according to local standards) or centrally. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following laboratory variables will be measured (Table 8). For haematology, see blinding procedures for eosinophil, basophil, and monocyte data in Section 6.3.

Table 8 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-Alkaline phosphatase (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-Gamma-glutamyl transferase (GGT)
U-Hb/Erythrocytes/Blood	S-Blood urea nitrogen
U-Glucose	S-Total Protein
U-Ketones	S-Hb1Ac
U-pH	S-NT-ProBNP
U-Bilirubin	S-Tryptase (only to be taken in event of suspected anaphylaxis see Appendix I)
U-Leukocytes	CCI [redacted]
U-Protein	Fibrinogen (plasma)
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 substudy	
Coagulation	
Endocrinology	
Serum FSH [b]	

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

[b] If needed to confirm post-menopausal status in female participants aged < 50 years.

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 = Haemoglobin; HbA1c = Hemoglobin A1c; NT-ProBNP = N-terminal pro-brain natriuretic peptide; RBC = Red blood cells; S = Serum; SoA = Schedule of activities; U = Urine.

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

Pregnancy Test

- Serum beta-human chorionic gonadotropin
- Urine human chorionic gonadotropin

Other Safety Tests

- HbA1c
- Hepatitis B (HBsAg, anti-HBs, and anti-HBc) and C antibodies
- HIV-1 and HIV-2 antibodies
- IGRA (TB test)
- Serum tryptase will only be taken in the event of suspected anaphylaxis (Appendix I)
- SARS-CoV-2 (serology and nucleic acid test)

It is recognised that frequent routine testing of asymptomatic participants for SARS-CoV-2 at visits SV3 onwards may be unnecessary and not actually contribute to participant safety. In regions where there is no community spread of covid infection (sporadic/imported cases or outbreaks only) and is expected to remain as such, the medical monitor, at the request of the PI of a site, may authorise a less demanding schedule of SARS-CoV-2 nucleic acid testing from SV3 onwards at that site. This authorisation may be ended by the medical monitor, at any time, should the local epidemiology change (or be expected to change).

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected by the investigator from informed consent throughout the intervention period and including the follow-up period.

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

8.3.2 Follow-up of AEs and SAEs

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

Adverse event variables

The following variables will be collected for each AE:

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

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication

PPD

8.3.3 Causality Collection

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

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

For COVID-related events, the investigator should add 'COVID' as part of the verbatim term.

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

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

Deterioration as compared to baseline in CSP-mandated laboratory values, spirometry values and vital signs should therefore only be reported as AEs if:

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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

8.3.6 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to understanding of MEDI3506 and may require close monitoring and rapid communication by the investigator to AstraZeneca. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of MEDI3506.

The following AESIs will be particularly monitored in this study:

- Hepatic function abnormality meeting the definition of HL as described in 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.
- 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

8.3.7 Hy's Law

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

8.3.8 Disease-Under Study

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

Acute exacerbations of COPD should be reported as AEs.

8.3.9 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The reference document for definition of expectedness/listedness is the IB for MEDI3506.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention.

8.3.10.1 Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as

SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.10) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.10.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 12 weeks after the last administration of study intervention.

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

8.3.11 Medication Error

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.1) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4 Overdose

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

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

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see section 8.3.9) and within 30 days for all other overdoses.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site.

8.5 Human Biological Samples

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

Samples will be stored for a minimum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
  - PK samples may be disposed of or anonymised by pooling. CCI

[redacted]

CCI

[redacted]

8.5.1 Pharmacokinetics

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

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Serum samples will be used to analyse the PK of MEDI3506. Samples collected for analyses of MEDI3506 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Samples from participants who received placebo may be analysed at minimum selected time points to confirm no dosing with MEDI3506 took place.

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

8.5.1.1 Determination of Study Intervention Concentration

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

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

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

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test 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. Full details of the methods used will be described in a separate report.

Anti-drug antibody samples may also be further tested for characterization of the ADA response, including possible assessment of neutralising antibody. No ADA samples will be collected after follow up period, except if considered necessary by the sponsor in the event of a potentially relevant adverse event in an individual patient.

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

8.5.3 Pharmacodynamics

There are no established PD measures for MEDI3506. CCI

8.6 CCI

8.6.1 CCI

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8.6.1.1 CCI

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8.6.1.2 CCI

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8.6.1.3 CCI

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8.6.1.4 Collection of Samples

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

8.6.2 CCI

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8.7 CCI

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8.8 Medical Resource Utilization and Health Economics

Not applicable.

8.9 Impact of COVID-19 Pandemic

To assess the impact of the COVID-19 pandemic on the study, sites will be asked to complete the pandemic impact questions in the eCRF at each study visit, according to the SoA (Section 1.3).

9 STATISTICAL CONSIDERATIONS

9.1 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_1: 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_1.

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 Hochberg procedure. Details will be described in the SAP.

9.2 Sample Size Determination

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 standard deviation of 250 mL) between the two 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).

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9.3 Populations for Analyses

The following populations are defined:

Table 9 Populations for Analysis

Population	Description
ITT population	Participants who are randomized and receive any study intervention. Participants will be analyzed according to their randomized study intervention group.
As-treated population	Participants who are randomized and receive any study intervention. Participants will be analyzed 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 intervention. Participants will be analyzed according to the study intervention they actually receive.

ITT = Intention-to-treat; PK = Pharmacokinetics.

The ITT population will be used to summarize all demographic and baseline characteristics, concomitant medications, and efficacy measures. The As-treated population will be used to summarize all safety measures (AEs, laboratory tests, ECG, and vital signs). The PK population will be used to summarize PK measures.

9.4 Statistical Analyses

All personnel involved with the analysis of the study will remain blinded until primary database lock and CSP deviations identified. Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 General Considerations

Efficacy analyses will be performed using the ITT population.

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, 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.

Demography and baseline characteristics will be summarized by study intervention group for the ITT population.

9.4.2 Efficacy

9.4.2.1 Primary Endpoints

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, for the ITT population. 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, eosinophil strata, background medication strata, 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. Estimates of the least square mean change from baseline in FEV_1 for each study intervention, and the difference between them, together with 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 as described in Section 9.1.

Additionally, the difference in mean change from baseline in FEV_1 at each study visit will be analyzed using a repeated measures mixed effects analysis of covariance model as described above, including all available data from all visits through to Week 28.

9.4.2.2 Secondary Endpoints

Time to first COPDCompEx event will be analyzed using a Cox proportional hazard model, with study intervention, eosinophil strata and background medication strata fitted as covariates. The data will also be displayed in a Kaplan-Meier plot. The COPDCompEx event rate will be analyzed using negative binomial regression, with the log(follow up time) included as an offset term. The dependent variable will be the number of COPDCompEx events through end of intervention, and the model will include study intervention group, eosinophil strata and background medication strata as fixed effects.

Subgroup Analyses:

Subgroup analyses may be performed. These will be described in the SAP, including a subgroup analysis of extent of emphysema on mean change from baseline in lung function at Week 28.

9.4.2.3 Exploratory Endpoints

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9.4.3 Safety

The occurrence of treatment-emergent AEs and SAEs will be described by system organ class, preferred term, severity, and relationship to the study intervention. Participants will be

counted only once for each preferred term, once for each system organ class, and by the highest severity of an event. Number of participants with elevated liver function tests that meet the HL definition will be evaluated. Laboratory evaluations will be summarized with descriptive statistics at each visit and change from baseline summarized for each post-baseline visit. Laboratory measurements will also be summarized based on the number and percentage of participants above or below a pre-specified threshold for each test. The number of participants with clinically significant abnormal ECG results based on investigators' judgments will be summarized at each visit. Change from baseline in vital signs will be summarized by visit.

9.4.4 Other Analyses

9.4.4.1 Patient Reported Outcomes

Change from baseline in objective cough measures at Week 12 will be analyzed using an analysis of covariance model, adjusting for baseline as a covariate and including study intervention, eosinophil strata and background medication strata as factors. Estimates of the least square mean change from baseline for each study intervention, and the difference between them, together with 80% CI, will be obtained from the model for each visit. Objective cough measurements may be log-transformed prior to analysis.

Other ePROs (BCSS, Cough VAS, SGRQ, CCI [redacted]) will be analyzed using a repeated measures mixed effects analysis of covariance model as described above for the primary analysis. For BCSS and Cough VAS, the average score over the previous 4 weeks will be analyzed.

9.4.4.2 CCI [redacted]

CCI [redacted]

9.4.4.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

PPD [redacted]

CCI [redacted] er with 80% CI and one-sided p-values, will be obtained from the model for each visit.

CCI [redacted]

CCI [redacted]

9.4.4.4 Additional Analyses

The incidence rate of positive antibodies to MEDI3506 will be reported by study intervention group. 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 PD, efficacy, and safety may be evaluated. MEDI3506 serum concentrations will be tabulated along with descriptive statistics. Mean and individual serum MEDI3506 concentration-time profiles will be plotted. Population PK modeling may be performed if data allow. The potential correlation between PK exposure and PD biomarkers, and efficacy/safety response may be evaluated.

CCI [redacted]

9.5 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. Additional details on the unblinding for interim analysis are provided in Section 6.3.3.1.

Details of any interim analyses, if conducted, will be included in the Interim Analysis Plan.

There are 3 planned analyses for this study. The Primary Analysis will occur once all participants have either completed the Week 12 assessments or withdrawn from the study. The End-of-Treatment analysis will occur once all participants have either completed the Week 28 assessments or withdrawn from the study. The Final Analysis will occur when all participants have completed the safety follow up period. Details relating to the unblinding for the Primary Analysis are in Section 6.3.3.1.

9.6 Data Monitoring Committee

An independent unblinded DSMB will perform evaluations of safety data, from this study and Studies D9181C00001 (in participants with asthma), D9182C00001 (in participants with atopic dermatitis) and D9183C00001 (in participants with diabetic kidney disease). Details of the composition of the DSMB, the data to be reviewed, and the frequency of the meetings can be found in the DSMB Charter. The DSMB will make any necessary recommendations to the sponsor regarding further conduct of the studies based on their evaluations of emerging data. A blinded study-specific safety committee (or Medical Monitor) will also review SAEs and SUSARs. For details on DSMB, refer to Appendix A 7.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the CSP and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The CSP, CSP amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the CSP will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

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

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

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

A 4 Data Protection

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

A 5 Committees Structure

An independent DSMB will be formed to evaluate safety data from concurrently conducted MEDI3506 Phase II clinical studies in other indications.

Unblinded review of safety data will be required for indications where the potential risks of MEDI3506 are high due to the disease under study and the common comorbidities of particular participant populations. Safety data from this study will be provided to the DSMB for oversight of all safety data. Details of the composition of the DSMB, the data to be reviewed, and the frequency of the meetings can be found in the DSMB Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspection and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

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

A 9 Study and Site Start and Closure

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

B 1 Definition of Adverse Events

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

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

B 2 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, run-in, intervention, washout, follow-up), that fulfils one or more of the following criteria:

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

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

Life Threatening

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

Hospitalisation

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

Important Medical Event or Medical Treatment

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

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

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

Severity Rating Scale:

The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 (based on the CTCAE criteria; NCI 2017) as defined below:

Grade 1 An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

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Grade 2 An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the participant.

Grade 3 A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.

Grade 4 An event, and/or its immediate sequelae, that is associated with an imminent risk of death.

Grade 5 Death as a result of an event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

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

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

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

B 4 Medication Error

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

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

Medication error includes situations where an error:

- occurred
- was identified and intercepted before the participant received the study intervention
- did not occur, but circumstances were recognised that could have led to an error

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

- Study intervention name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Study intervention not administered as indicated, for example, wrong route or wrong site of administration
- Study intervention not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet

- Study intervention not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding RTSM system errors)
- Wrong study intervention administered to participant (excluding RTSM system errors)

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

- Errors related to or resulting from the RTSM system - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed study intervention dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and CCI [redacted], or standard of care medication in open label studies, even if an AstraZeneca product

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

The investigator:

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

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

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

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

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

Appendix D CCI

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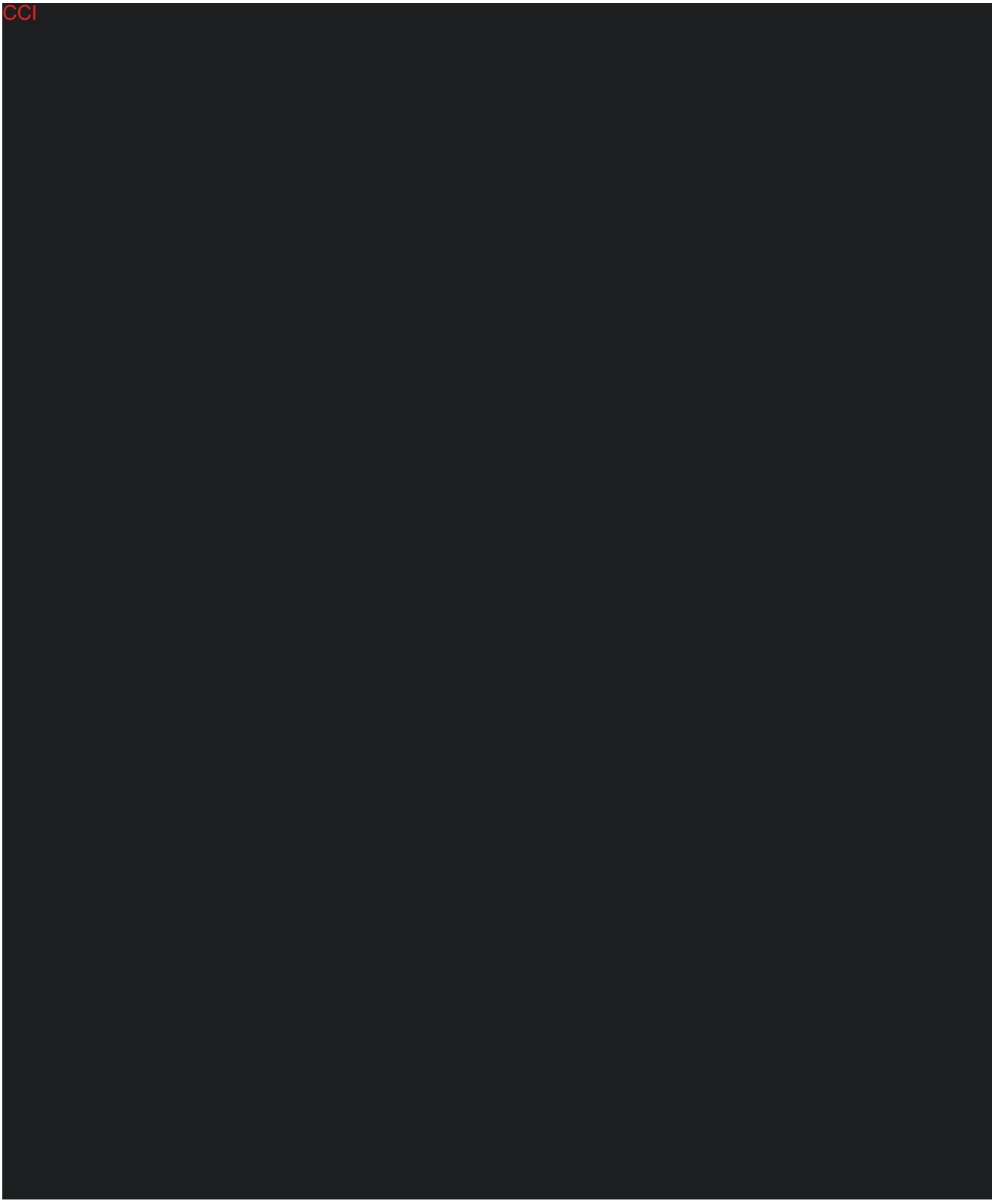

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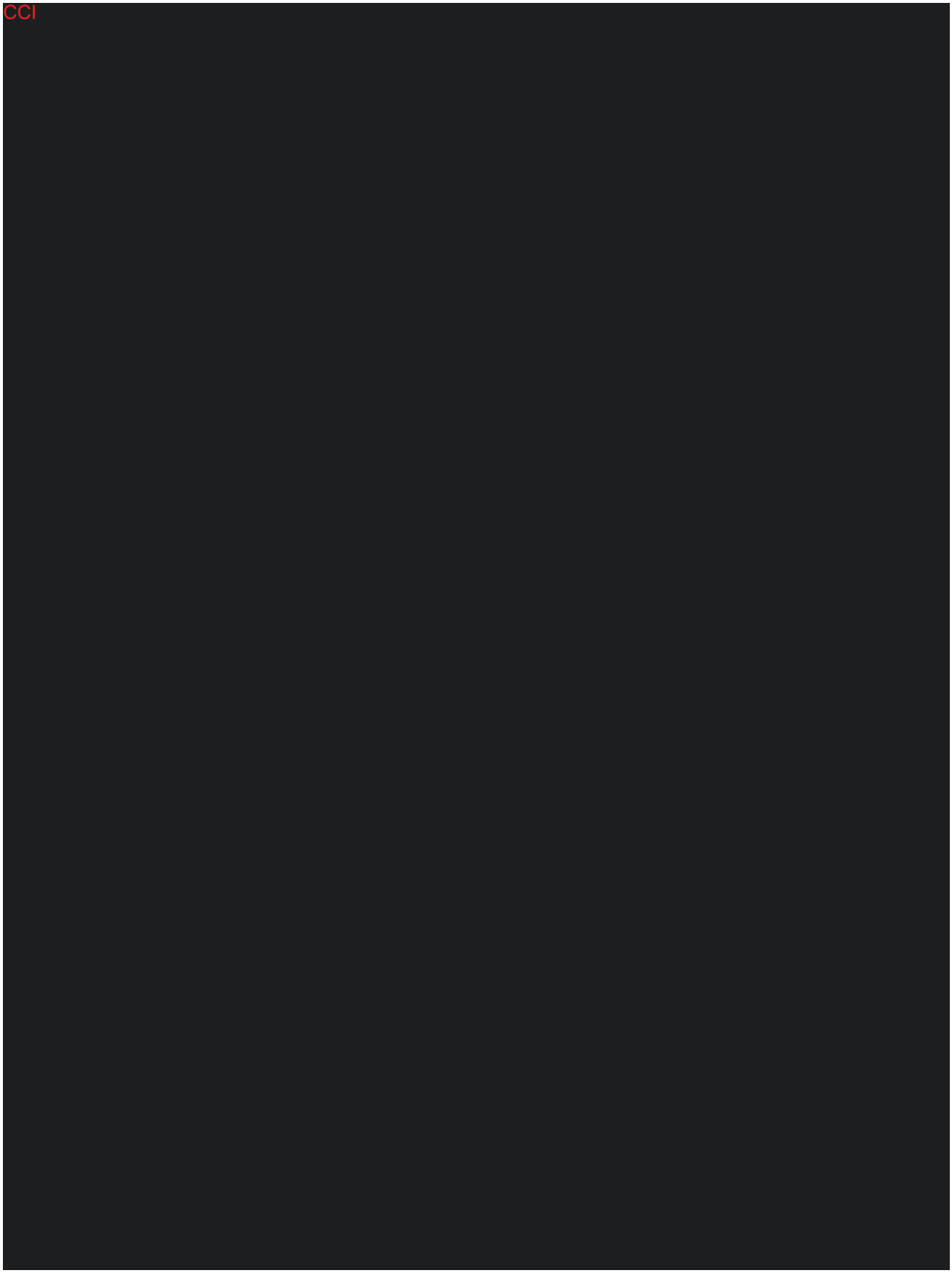

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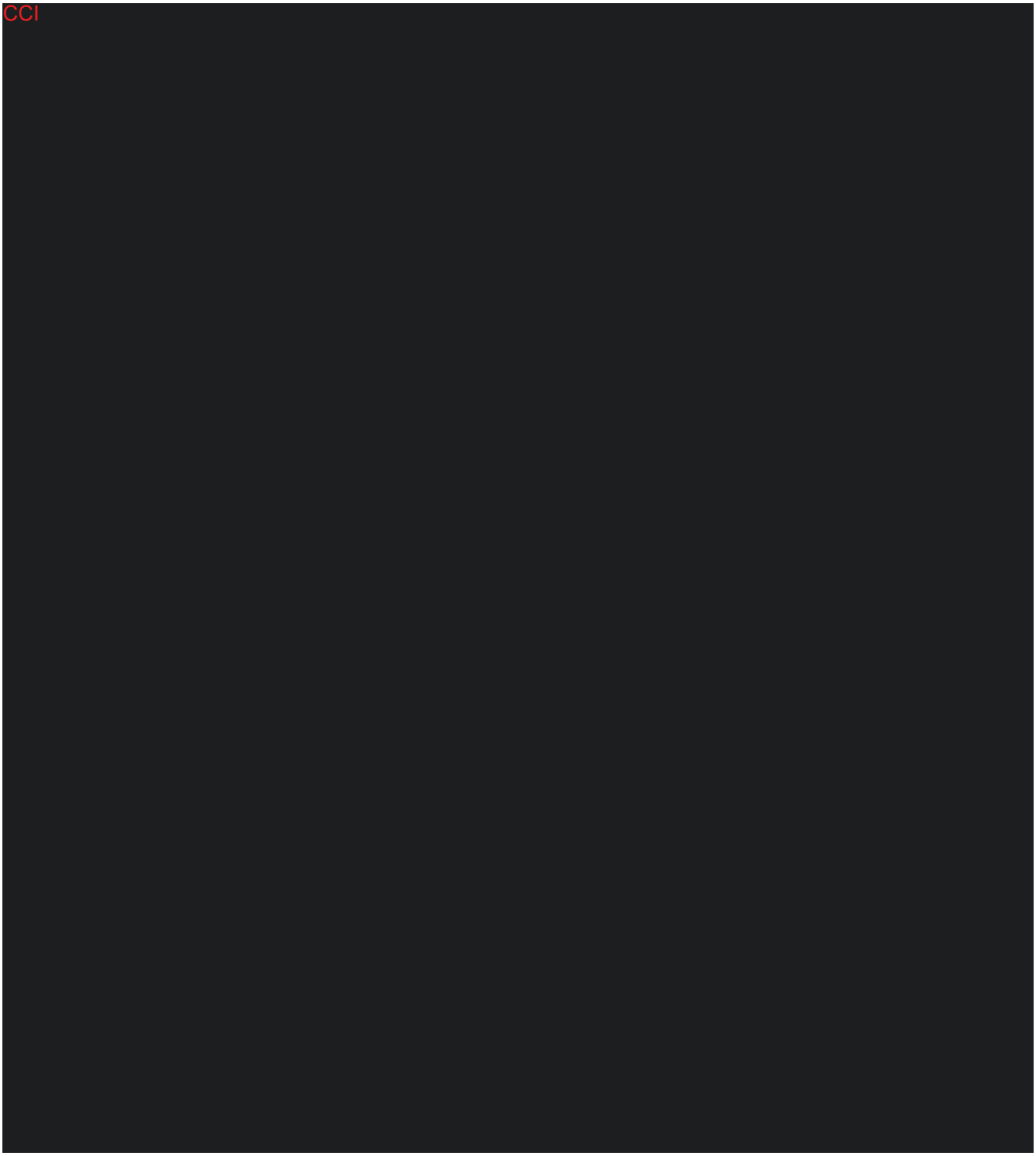
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Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

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

Specific guidance on managing liver abnormalities can be found in Section 8.3.7 of the CSP.

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

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

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

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

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

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law (HL)

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

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

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

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

Central Laboratories Being Used:

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

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay.

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

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

Local Laboratories Being Used:

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

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria (see Appendix E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

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

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention

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

- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition
- The AstraZeneca Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the AstraZeneca Study Physician.
  - Complete the three Liver eCRF Modules as information becomes available

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

PPD

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

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

As soon as possible after the biochemistry abnormality was initially detected, the AstraZeneca Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug induced liver injury caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF

If the alternative explanation is an **AE/SAE: update** the previously submitted PHL SAE and AE eCRFs accordingly with the **new information** (reassessing event term; causality and seriousness criteria) following **the AstraZeneca** standard processes.

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

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

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

- Provides any further update to the previously submitted SAE of PHL, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory tests

Hy's Law Laboratory Kit for Central Laboratories

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

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

Ab = Antibody; CD-transferrin = Carbohydrate deficient transferrin; CMV = Cytomegalovirus; DNA = Deoxyribonucleic acid; EBV = Epstein-Barr virus; GGT = Gamma-glutamyl transferase; HAV = Hepatitis A virus; HBc = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HEV = Hepatitis E virus; HSV = Herpes simplex virus; Ig = Immunoglobulin; RNA = Ribonucleic acid.

PPD

E 7 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case Definition and Phenotype Standardization in Drug-Induced Liver Injury. Clin Pharmacol Ther 2011;89(6):806-15.

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

Appendix F Contraception Guidance

Women are considered to be of childbearing potential unless they meet either of the criteria, as follows:

- Surgically sterilized (including bilateral tubal ligation, bilateral oophorectomy, or
- hysterectomy), or
- Post-menopausal.

For women aged < 50 years, post-menopausal is defined as having both:

- A history of ≥ 12 months amenorrhea, without an alternative cause, following cessation of
- exogenous sex-hormonal treatment and,
- A follicle-stimulating hormone level in the post-menopausal range.

For women aged ≥ 50 years, post-menopausal is defined as having a history of ≥ 12 months amenorrhea, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in Table 10 below.

Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

Table 10 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	Combined (estrogen and progestogen containing hormonal contraception) • Oral (combined pill) • Injectable • Transdermal (patch) • Progestogen-only hormonal contraception • Desogestrel

[a] This is also considered a hormonal method.
[b] With appropriate post-vasectomy medical testing of surgical success (ie, absence of sperm in ejaculate).
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant.

Appendix G Major and Minor Symptoms of COPD

The following questions and response options (or their translations) will be presented by the eDiary device to capture major and minor symptoms of COPD.

Question: How breathless have you been in the last 24 hours?

Response Options:

- Less breathlessness than usual
- Usual level of breathlessness
- More breathless than usual

Question: How much mucus (phlegm) did you have in the last 24 hours?

Response Options:

- Less than usual or no mucus (phlegm)
- Usual amount of mucus (phlegm)
- More mucus (phlegm) than usual

Question: What color was your mucus (phlegm) in the last 24 hours?

Response Options:

- No mucus (phlegm)
- Mucus (phlegm) was the usual color
- Mucus (phlegm) was a darker or a different color than usual

Question: How much have you coughed in the last 24 hours?

Response Options:

- Less cough than usual
- Usual level of cough
- More cough than usual

Question: How much have you wheezed in the last 24 hours?

Response Options:

- Less wheeze than usual
- Usual level of wheeze

- More wheeze than usual

Question: Have you had a sore throat in the last 24 hours?

Response Options:

- No
- Yes, I had a sore throat

Question: Have you had the symptoms of a cold such as a runny nose or nasal congestion in the last 24 hours?

Response Options:

- No symptoms of a cold
- Yes, I had symptoms of a cold

Question: Have you had a fever in the last 24 hours?

Response Options:

- No
- Yes, I had a fever

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

National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (Category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST 1 OF THE FOLLOWING:
   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
   (b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence).
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3 Reduced BP after exposure to known allergen for that participant (minutes to several hours):
   (a) Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

For the purpose of AE reporting, the above criteria should be used to guide retrospective judgment as to whether an event was true anaphylaxis. Guidance on the recognition of possible anaphylaxis at the time of the event is provided (Appendix I).

PPD

Appendix I Signs and Symptoms and Management of Acute Anaphylaxis

Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis. Local or national guidelines for the recognition and management of acute anaphylaxis should be followed where available. Where not available, guidance is provided below.

I 1 Signs and Symptoms of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

- Diffuse erythema.
- Pruritus.
- Urticaria and/or angioedema.
- Bronchospasm.
- Laryngeal edema.
- Hypotension.
- Cardiac arrhythmias.
- Feeling of impending doom.
- Unconsciousness.
- Shock.

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles.
- Rhinorrhea.
- Change in voice.
- Metallic taste.
- Nausea, vomiting, diarrhea, abdominal cramps, and bloating.
- Light-headedness.
- Headache.
- Uterine cramps.
- Generalized warmth.

PPD

I 2 Management of Acute Anaphylaxis

I 2.1 Immediate Intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation.

2 Administer epinephrine intramuscularly every 5 to 15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

I 2.2 Possibly Appropriate, Subsequent Measures Depending on Response to Epinephrine

1 Place participant in recumbent position and elevate lower extremities.

2 Establish and maintain airway.

3 Administer oxygen.

4 Establish venous access.

5 Normal saline IV for fluid replacement.

I 2.3 Specific Measures to Consider after Epinephrine Injections, Where Appropriate

1 Consider epinephrine infusion.

2 Consider H1 and H2 antihistamines.

3 Consider nebulized beta-2 agonist [eg, albuterol (salbutamol)] for bronchospasm resistant to epinephrine.

4 Consider systemic corticosteroids.

5 Consider vasopressor (eg, dopamine).

6 Consider glucagon for participant taking b-blocker.

7 Consider atropine for symptomatic bradycardia.

8 Consider transportation to an emergency department or an intensive care facility.

9 For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

If a suspected anaphylactic reaction occurs during or within a 24-hour period after administration of study intervention, blood samples for serum tryptase should be collected as soon as possible after the event, at 60 ± 30 minutes after the event, at discharge, and between 2 and 4 weeks post discharge. Immediate care of the participant and treatment of the reaction must take priority over collecting blood samples.

Adapted from Kemp et al 2008.

Appendix J Example of Patient COVID-19 Screening Questionnaire

1 Have you experienced unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and/or new loss of taste or smell within the past 14 days?

2 Have you been in contact with anyone who is sick or with symptoms in the last 14 days? **Note to site:** probe on the same symptoms as Q1.

3 Have you been exposed to someone diagnosed with COVID-19 in the last 14 days?

4 Have you been practicing social distancing over the last 14 days? **Note to site:** please refer to region/city/country regulations.

5 Have you travelled in the last 14 days, if so, where? **Note to site:** recent travel including to countries/regions with Centers for Disease Control and Prevention Level 2 or higher travel warning, or equivalent, or known COVID-19 hot spots.

6 Have you been in isolation or quarantine for any reason in the past 14 days?

7 Have you been diagnosed with COVID-19 at any time, if so, where and when?

8 Have you been vaccinated against COVID-19?

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

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

K 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections K 2 to K 6. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

K 2 Rescreening of Participants To Reconfirm Study Eligibility

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

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in the SoA (see Section 1.3) the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 5.1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

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

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

K 4 Telemedicine Visit to Replace On-site Visit (where applicable)

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication, and adherence to the eDiary and ePRO measures to be reported and documented.

K 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the participant or his/her caregiver. The option of at-home or remote location IP administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

Section K 5.1 to be used only when applicable for the IP formulation being used, eg, with injectable biologics.

K 5.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service should administer the IP at the participant's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

K 5.2 At-home or Remote Location IP Administration by the Participant or His/Her Caregiver

Prior to at-home or remote location IP administration the investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP

administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

K 6 Data Capture During Telemedicine or Home / Remote Visits

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

Appendix L Abbreviations

Abbreviation or special term	Explanation
ACM	Ambulatory Cough Monitoring
ADA	Anti-drug Antibody
AE	Adverse Event
AECOPD	Acute Exacerbation of Chronic Obstructive Pulmonary Disease
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HBs	Antibody to hepatitis B core antigen
AO	Airwave Oscillometry
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area under the Concentration Time Curve
$AUC_{0\text{-}4\ weeks}$	Area under the Concentration Time Curve from Weeks 0 to 4
AX	Area of Reactance
B	Blood
BCSS	Breathlessness, Cough and Sputum Scale
BD	Bronchodilator
BMI	Body mass index
BP	Blood Pressure
CCI [redacted]	
CAT	COPD Assessment Test
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
$C_{max,ss}$	Maximum Concentration at Steady State
COPD	Chronic Obstructive Pulmonary Disease
COPDCompEx	COPD Composite Exacerbations
COVID-19	Coronavirus disease 2019
CCI [redacted]	
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	

Abbreviation or special term	Explanation
d	Day
DBP	Diastolic Blood Pressure
CCI [redacted]	
DSMB	Data Safety Monitoring Board
E/A	Exacerbation Assessment
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
E/D	Early Study Intervention Discontinuation Visit
eDiary	Electronic Diary
ePRO	Electronic Patient Reported Outcome
EOT	End of Treatment
E-RS:COPD	Evaluating Respiratory Symptoms of COPD
ERS	European Respiratory Society
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Prac ice
GGT	Gamma-glutamy Transferase
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBc	He titis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HCP	Healthcare Provider
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HRT	Hormone Replacement Therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroids

Abbreviation or special term	Explanation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IGRA	Interferon Gamma Release Assay
IL-33	Interleukin-33
IMP	Investigational Medicinal Product
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-Treat
IV	Intravenous
LABA	Long Acting Beta 2 Agonist
LAMA	Long Acting Muscarinic Receptor Antagonist
LTBI	Latent tuberculosis infection
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MMP	Matrix Metalloproteinases
CCI	
NIMP	Non-investigational Medicinal Product
NT-proBNP	N-terminal pro-brain natriuretic peptide
OCS	Oral Corticosteroids
PD	Pharmacodynamics
PDE4 Inhibitor	Phospohidiesterase-4 Inhibitor
PEF	Peak Expiratory Flow
CCI	
PHL	Potential Hy's Law
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
RTSM	Randomization and Trial Supply Management
S	Serum
SABA	Short-Acting Beta Agonists

Abbreviation or special term	Explanation
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonists
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
SC	Subcutaneous
SGRQ	St George's Respiratory Questionnaire
SID	Subject Identification
SoA	Schedule of Activities
SOP	Standard operating procedure
CCI [redacted]	
CCI [redacted]	
CCI [redacted]	
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Study Visit
TB	Tuberculosis
TBL	Total Bilirubin
TC	Telephone Contact
TPV	Third party vendor
CCI [redacted]	
U	Urine
UK	United Kingdom
ULN	Upper Limit of Normal
V	Visit
VAS	Visual Analogue Scale
w/v	Weight per Volume

Appendix M Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 4 (23 July 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Amendment:

To reflect emerging evidence supporting coexistence of significant mucus hypersecretion in all extents of emphysema, to adjust for the impact of COVID-19 on exacerbation frequency globally, and to clarify wording on various points.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 5.2 (Exclusion criteria) Section 2.2 (Background) and Section 2.3.1 (Risk Assessment) Section 3 (Objectives) Section 4.2 (Scientific rationale for study design)	Remove exclusion criterion 4 (predominant emphysema). Provide rationale for change. Additional secondary CCI [redacted] objective to assess response to MEDI3506 by extent of emphysema on baseline CT scan in main study. Provide rationale for change.	Emerging evidence supporting coexistence of significant mucus hypersecretion in all extents of emphysema (Dunican et al 2021; Kim et al 2021) and therefore amended to investigate impact of MEDI3506 in all patients regardless CCI [redacted]	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.1.9 (Chest CT) Section 9.4.2.2 (Subgroup analyses)	Removal of reference to exclusion criteria for extent of emphysema. Addition of emphysema subgroup analysis for primary endpoint.		
Table 2 (Screening Procedures) and Section 4.1.1 (Study [and Sub-Study] Conduct and Planned Mitigations During COVID-19 Pandemic)	PCR analysis changed to nucleic acid analysis.	To account for countries that use a test equivalent to PCR that is not technically PCR.	Non-substantial
Section 4.1 (Overall Design)	Added information in the event that automated calculation of emphysema percentage is not technically possible.	For clarification.	Non-substantial
Section 4.2.1 (Rationale for study population)	Update to text on how BCSS inclusion criterion helps to identify patients most likely to respond to MEDI3506. (Criterion itself unchanged).	For clarification.	Non-substantial
Section 5.1 (Inclusion criteria) Section 4.1 (Overall design) Section 4.2.1 (Rationale for study population)	Change to ≥ 1 exacerbation of COPD in 24 months from 12 months. Rationale for change to exacerbation inclusion criteria.	Impact of COVID-19 on exacerbation frequency globally due to changed behaviour/shielding of vulnerable patients with respiratory disease. During the ongoing COVID-19 pandemic, as a result of changed patient behaviour, there has been a significant reduction in exacerbation frequency compared with previous years. Data from the UK suggested a 50% reduction in exacerbation related-hospital admissions compared with pre-pandemic	Non-substantial

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Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		(Alsallakh et al 2021; Tan et al 2020), and a 39% reduction in primary care consultations related to COPD. This picture is replicated in other countries. Leaving the requirement for at least one moderate or severe exacerbation in the previous 12 months unchanged would lead to the exclusion of patients who in previous years would have been included.	
Section 5.1 (Inclusion criteria)	Change BMI to 18-35 kg/m^2 from 19-35 kg/m^2.	Correcting error in wording to all w all patients of BMI range within normal limits to be included in study.	Non-substantial
Section 5.2 (Exclusion criteria)	Clarify wording on lung resection exclusion.	To better clarify exclusion for lung resection is based upon significant resection (pneumonectomy) which would impact upon lung function or where lung volume reduction surgery has been carried out where COPD was the indication. Clarification to allow stable patients who have previously undergone lobar or wedge resection due to causes other than COPD.	Non-substantial
Section 5.2 (Exclusion criteria)	Clarification on testing for hepatitis C infection.	Provide greater clarification that positive HCV antibodies would exclude a participant from the study.	Non-substantial

BCSS = Breathlessness, Cough and Sputum Scale; BMI = Body mass index; COPD = Chronic obstructive pulmonary disease; COVID-19 = Coronavirus disease 2019; CT = Computed tomography; HCV = Hepatitis C virus; PCR = Polymerase chain reaction; UK = United Kingdom.

Amendment 3 (01 June 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

To clarify wording on various points, to remove unnecessary tests, and add flexibility in regard to SARS-CoV-2 testing.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 (Schedule of Activities) Section 5.1 (Inclusion Criteria; Criterion 14)	Clarification that pregnancy tests should be carried out in WOCBP only.	Removal of unnecessary testing of women not of childbearing potential that causes inconvenie ce to patients when not cli ically relevant or appropriate and causes co f sion to site staff.	Non-substantial
Section 1.3 (Schedule of Activities)	Clarified urine pregnancy tes at SV2 is not required if CT scan is not performed.	Unnecessary test in that circumstance.	Non-substantial
Section 1.3 (Schedule of Activities), Section 4.1.1 and Section 8.2.6 (Clinical Safety Laboratory Assessments)	Permitted local laboratories to perform SARS-Cov-2 nucleic acid testing (nasopharyngeal swab), as well as the central laboratory and permit less frequent testing dependent on pr valence of covid infection.	To avoid delays in this result and to avoid unnecessary duplication where local procedures also require local testing. To permit less frequent testing in areas of low or very low incidence after agreement with medical monitor.	Non-substantial
Section 5.1 (Inclusion Criteria)	Inclusion Criterion 3: Clarification of influenza and pneumococcal vaccine requirements	To ensure vaccination requirements are compatible with national practices and seasonal vaccine availability.	Non-substantial
Section 5.2 (Exclusion Criteria; Criterion 25)	Clarification of a positive IGRA test in the context of treated latent TB infection.	Participants with a positive IGRA test and no active disease, who have undergone or who undergo full treatment for LTBI are not excluded from the study by virtue of a positive test (which can remain positive despite treatment).	Non-substantial
Section 5.2 (Exclusion Criteria)	To remove unnecessary effective prohibition on	Exclusion Criterion 42 serves to limit total radiation exposure to	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 5.4 (Screen Failures) Section 8.1.9 (Chest CT)	CCI [redacted]	CCI [redacted]	
Section 5.4 (Screen Failures)	In the case of re-screening, to permit echocardiogram and IGRA (TB test) results no more than 3 months old, to be re-used.	Results are not likely to have changed significantly within a 3 month period unless there has been a new significant medical event (which would be captured within Exclusion Criterion 3). These tests are costly and time-consuming both for patient and/or perator.	Non-substantial
Section 6.3.2 (Methods to Ensure Blinding)	Included that the randomisation schedule may be provided to limited personnel.	To facilitate in-stream analysis of PK and ADA samples	Non-substantial
Section 6.5.6 (COVID-19 vaccination)	Clarification of information to be recorded in the event of a participant receiving a COVID-19 vaccine	To ensure necessary data is captured.	Non-substantial
Section 8.1.8.8	Clarified that agreement to participate in t e Study Participant F dback Questionaire will be included in the ICF	Clarification	Non-substantial
Section 8.3.10 (Pregnancy) Appendix B	Congenital abnormality changed to congenital anomaly	To meet regulatory requirements on good pharmacovigilance practices	Non-substantial
Section 8.5.1 (Pharmacokinetics)	Clarification of processing of PK samples from participants who received placebo.	Clarification added to avoid unnecessary analysis on samples where no IMP administered.	Non-substantial
Section 8.5.2 (Immunogenicity Assessments)	Included that neutralising antibody may also be assessed	To further assess immunogenicity	Non-substantial
Throughout	Minor typographical changes	For clarification	Non-substantial

ADA = Anti-drug Antibody; COVID-19 = Coronavirus disease 2019; CT = Computed tomography; ICF = Informed Consent Form; IMP = Investigational medicinal product; LTBI = Latent tuberculosis infection; PK = Pharmacokinetic; SARS-Cov-2 = Severe acute respiratory syndrome coronavirus 2; SV = Study Visit; TB = Tuberculosis; WOCBP = Women of childbearing potential.

Amendment 2 (08-Feb-2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the EU because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

To clarify restrictions applicable to newly available vaccines against COVID-19 and to remove the induced sputum and capnography sub-studies.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis 1.3 Schedule of Activities 2.3.1 Risk Assessment 3 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5 Study Population 5.1 Inclusion Criteria 5.2 Exclusion Criteria 8.1.1 Clinic Spirometry CCI [redacted] 8.6.1.5 Induced Sputum 9.2 Sample Size Determination	CCI [redacted]	As a result of the COVID-19 pandemi sputum induction and required local processes have proven not to be feasible at the required number of sites. Spontaneous sputum sampling remains a part of the protocol.	Non-substantial
1.1 Synopsis 1.3 Schedule of Activities 3 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5 Study Population 5.1 Inclusion Criteria 8.1.12 Capnography Sub-study 9.2 Sample Size Determination	CCI [redacted] prior to inclusion of any participants in that sub-study	Given the practical difficulties for sites conducting this study during the COVID-19 pandemic, the exploratory sub-study has been removed to reduce site burden.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.3 Schedule of Activities	Addition of PK and immunogenicity samples at SV11	To better characterize the PK profile	Non-substantial
3 Objectives and Endpoints	Added exploratory endpoints CCI [redacted]	Correction of erroneous omission in protocol (data was collected in previous version)	Non-substantial
4.1.1.1 Vaccination Against COVID-19 5.2 Exclusion Criteria 6.5.5 Restricted and Prohibited Medications	Addition of instructions on when COVID-19 vaccination should be given to study participants	To respond to recent emergency use authorizations of COVID-19 vaccines and mitigate any potential risks	Non-substantial
4.4.1 Study Stopping Criteria	Addition of specific study stopping criteria (individual IP discontinuation criteria already present)	To comply with a request from the FDA	Non-substantial
5.2 Exclusion Criteria	Exclusion Criterion 15: Addition of clarification	To comply with a request from n Ethics Committee	Non-substantial
5.2 Exclusion Criteria	Exclusion Criterion 9(g): Removing requirement for surveillan CT s ans as exclusion for main study Exclusion Criterion 43: Adding need for future CT scans (eg, surveillance scans) as exclusion for CT sub-study	Given available scientific literature on natural history of chest CT findings requiring CT scan, and lack of relationship to mechanism of action, it was considered that exclusion was unnecessary. However, it was recognized that the total radiation burden of surveillance scans should not be added to by end of study scans.	Non-substantial
5.2 Exclusion Criteria 6.5.5 Restricted and Prohibited Medications	Exclusion Criterion 34(d): Added clarification for vaccines with adenoviral vectors that are unable to replicate	To clarify that these are not considered live or attenuated	Non-substantial
6.5.6 COVID-19 Vaccination 8.2.1 Medical, Surgical and COPD History	Added clarification on recording of COVID-19 vaccination	To ensure this information is accurately recorded	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix J Example of Patient COVID-19 Screening Questionnaire	New question added for COVID-19 vaccination	To provide an example question for sites on COVID-19 vaccination	Non-substantial

COPD = Chronic Obstructive Pulmonary Disease; COVID-19 = Coronavirus disease 2019; CT = Computed Tomography; FDA = Food and Drug Administration; PK = Pharmacokinetics; SV = Study Visit.

Amendment 1 (01-Oct-2020)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The FDA recommended changes to the protocol, including amending the study intervention discontinuation criteria and using a standardized toxicity grading scale.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.3 Schedule of Activities	Adjustment of footnotes regarding timing of repeat attempts in case of failure to successfully obtain spontaneous and induced sputum samples	To improve flexibility for sites and thereby minimise the chance of failure to obtain a sample.	Non-substantial
5 Study Population	Addition of text regarding participants who meet eligibility criteria for main study but not sub-study.	To clarify that participants found to be ineligible for the sub-study should not automatically be discontinued from the main study.	Non-substantial
5.1 Inclusion Criteria	Correction of typographical error in Inclusion Criterion 6	-	Non-substantial
5.2 Exclusion Criteria	Addition of clarification regarding quantitative assessment of CT scan showing emphysema in Exclusion Criterion 4 (c).	To avoid confusion with other quantitative assessments of CT scan.	Non-substantial
5.2 Exclusion Criteria	Correction of typographical error in Exclusion Criterion 34 (h)	-	Non-substantial
6.2.2 Dose Preparation Steps	Correction of a typographical error	-	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
7.1 Discontinuation of Study Intervention	Criteria for discontinuation amended.	To address recommendations from the FDA.	Non-substantial
8.2.5 Echocardiogram	Addition of detail regarding how the echocardiogram should be performed.	To ensure consistency between sites.	Non-substantial
8.2.6 Clinical Safety Laboratory Assessments	Addition of urine specific gravity to Table 8 (Laboratory Safety Variables)	Correction of omission in original protocol.	Non-substantial
8.2.6 Clinical Safety Laboratory Assessments	Removal of 'Hepatitis A' from other safety tests.	Correction of erroneous inclusion in original protocol.	Non-substantial
Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Replacement of Intensity Rating Scale with Severity Rating Scale based on the CTCAE criteria.	To address recommendations from the FDA	Non-substantial

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration.

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