Clinical Study Protocol	
Study Intervention	MEDI3506
Study Code	D9181C00001
Amendment	4.0
Date	08 March 2022

A Phase II, Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of MEDI3506 in Adult Participants with Uncontrolled Moderate-to-severe Asthma

Sponsor Name: AstraZeneca

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

Regulatory Agency Identifier Numbers:

IND number 140910

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

Protocol Number: D9181C00001

Amendment Number: 4.0

Study Intervention: MEDI3506 and placebo

Study Phase: II

Short Title: Study to Assess the Efficacy and Safety of Subcutaneously Injected MEDI3506 in Adults with Uncontrolled Moderate-to-severe Asthma

Acronym: FRONTIER-3

Medical Monitor Name and Contact Information will be provided separately

International co-ordinating investigator

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

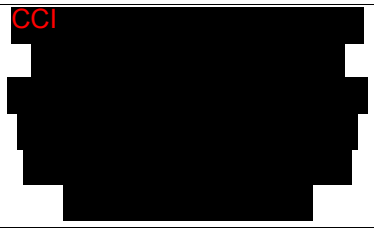
DOCUMENT HISTORY	
Document	**Date**
Amendment 4.0	08 March 2022
Amendment 3.0	25 May 2021
Amendment 2.0	23 February 2021
Amendment 1.0	19 October 2020
Original Protocol	21 May 2020

Amendment 4.0 (08 March 2022)

Overall Rationale for the Amendment:

Changes from Global Protocol Amendment 3.0

The principal reason for this amendment is to remove Part B, the airway hyperresponsiveness and remodelling study.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout	Removal of references to and text regarding Part B, including SV3 which only applied to Part B	Given the challenges of conducting this study the sponsor has, prior to any participant participating in Part B, decided to defer assessment of the effects of MEDI3506 on airway hyperresponsiveness and remodelling until later in development of MEDI3506	Substantial
Throughout	Removal of occurrences of 'Part A'	As Part B has been removed, Part A is the entirety of the study	Substantial
Section 1.3 Schedule of Activities	CCI 	CCI 	Substantial
Section 2.3.1 Risk Assessment	Updated rationale for risk of progression of heart failure	To provide information based on current data	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.1 Overall Design; Section 9.2 Sample Size Determination	Change to permit not capping randomisation of participants not included in exploratory cough sub-study solely to achieve target sample size of the sub-study	To avoid completion of exploratory sub-study delaying completion of study overall	Non-substantial
Section 5.1 Inclusion Criteria	Criterion 11: Increased the maximum permitted BMI to 40 kg/m^2	To maintain consistency with other MEDI3506 studies in context of other exclusion criteria	Substantial
Section 5.1 Inclusion Criteria	Criterion 19: Changed historic exacerbation requirement from one in 12 months to one in 24 months	To adapt to sustained fall in real world exacerbation rates secondary to the ongoing COVID-19 pandemic	Substantial
Section 5.2 Exclusion Criteria	Criterion 1: Removed the exclusion of all participants who test positive for SARS-CoV-2 at SV1. All participants who test positive at SV2 continue to be excluded.	To permit participants who test positive for SARS-CoV-2 at SV1, but negative at SV2 and who do not have symptoms meeting any other exclusion criterion to be randomised.	Substantial
Section 5.2 Exclusion Criteria	Criterion 3: Rewritten	Revised text to be clearer and consistent with other AstraZeneca studies	Substantial
Section 5.2 Exclusion Criteria; Section 1.3 Schedule of Activities, Table 1 Footnote i	Criterion 5: Removal of entire criterion which excluded participants with an NT-proBNP above the upper limit of normal.	Not considered to provide additional benefit to participant safety given other mitigations, including screening echocardiograms	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 5.2 Exclusion Criteria	Criterion 13: Removed the reference to HbA1c	To permit investigator judgement as to whether Type 2 diabetes is well controlled (and hence not exclusionary) and to maintain consistency with other MEDI3506 studies	Substantial
Section 6.5.5 COVID-19 Vaccination	Removed dose from list of information to be recorded	Information is generally not available	Non-substantial
Section 8.1.5 Asthma Exacerbations	Adjustment of requirements of acceptable documentation of historical exacerbations.	Response to changes in practical management of real world asthma exacerbations in context of COVID-19 pandemic	Non-substantial
Section 8.5.1 Human Biological Samples, Appendix D 1 Use/Analysis of DNA, Appendix D 2 Genetic Research Plan and Procedures	Specified samples will be retained for 15 years after the end of the study	To align with EU guidelines for data storage	Non-substantial
Section 8.5.2 Pharmacokinetics	Removed text specifying how many PK samples would be collected	Information is available in the Schedule of Assessments	Non-substantial
Section 8.5.5 Collection of Mandatory Samples for Biomarker Analysis	Changed IL-33 isoform sample from nasal epithelium to nasal lining fluid and mRNA transcriptome sample from nasal to nasal mucosal sample.	Clarification	Non-substantial
Appendix A 6 Data Quality Assurance	Changed the length of time records and documents are stored from 15 to 25 years after study completion	To align with EU guidelines for data storage	Non-substantial

BMI = body mass index; COVID-19 = coronavirus disease 2019; EU = European Union; HbA1c = haemoglobin A1c; IL-33 = interleukin-33; NT-proBNP = N terminal prohormone of B type natriuretic peptide; PK = pharmacokinetics; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SV = study visit.

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3
TABLE OF CONTENTS 6
1 PROTOCOL SUMMARY 11
1.1 Synopsis 11
1.2 Schema 13
1.3 Schedule of Activities 15
2 INTRODUCTION 23
2.1 Study Rationale 23
2.2 Background 23
2.3 Benefit/Risk Assessment 24
2.3.1 Risk Assessment 24
2.3.1.1 Study Conduct During COVID-19 Pandemic 28
2.3.1.2 COVID-19 Mitigations 28
2.3.1.3 Vaccination Against COVID-19 30
2.3.2 Benefit Assessment 31
2.3.3 Overall Benefit: Risk Conclusion 31
3 OBJECTIVES AND ENDPOINTS 32
4 STUDY DESIGN 35
4.1 Overall Design 35
4.2 Scientific Rationale for Study Design 37
4.2.1 Rationale for Endpoints 38
4.2.1.1 Primary Endpoints 38
4.2.1.2 Secondary and Safety Endpoints 38
4.2.1.3 Exploratory Endpoints 38
4.2.2 Rationale for Study Population 38
4.2.3 Participant Input into Design 39
4.3 Justification for Dose 39
4.4 End of Study Definition 40
4.4.1 Study Stopping Criteria 40
5 STUDY POPULATION 41
5.1 Inclusion Criteria 41
5.2 Exclusion Criteria 44
5.3 Lifestyle Considerations 48
5.3.1 Meals, Dietary Restrictions, and Caffeine 48
5.3.2 Activity 49
5.4 Screen Failures 49
6 STUDY INTERVENTION 49

6.1 Study Interventions Administered 50
6.2 Preparation/Handling/Storage/Accountability of Interventions 50
6.2.1 Study Intervention Inspection 51
6.2.2 Dose Preparation Steps 51
6.2.2.1 Treatment Administration 52
6.2.2.2 Monitoring Dose Administration 53
6.2.3 Accountability 53
6.3 Measures to Minimise Bias: Randomisation and Blinding 53
6.3.1 Methods for Assigning Treatment Groups 53
6.3.2 Methods to Ensure Blinding 54
6.3.3 Methods for Unblinding 54
6.4 Study Intervention Compliance 55
6.5 Concomitant Therapy 55
6.5.1 Rescue Medicine 56
6.5.2 Required Medications 56
6.5.3 Medication Withhold Periods 56
6.5.4 Prohibited Medications 57
6.5.5 COVID-19 Vaccination 58
6.6 Dose Modification 58
6.7 Intervention after the End of the Study 58
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 58
7.1 Discontinuation of Study Intervention 58
7.1.1 Missed doses 59
7.2 Participant Withdrawal from the Study 59
7.3 Lost to Follow-up 60
8 STUDY ASSESSMENTS AND PROCEDURES 60
8.1 Efficacy Assessments 61
8.1.1 In-clinic Spirometry 61
8.1.1.1 General requirements 61
8.1.2 At-home Spirometry 63
8.1.3 Airwave Oscillometry 63
8.1.4 Fractional Exhaled Nitric Oxide 64
8.1.5 Asthma Exacerbations 64
8.1.6 CompEx 66
8.1.7 VitaloJAK Cough Monitor (Exploratory Cough Sub-study Only) 67
8.1.8 Participant Reported Outcome Questionnaires 67
8.1.8.1 Daily eDiary 68
8.1.8.2 Cough Visual Analogue Scale (Exploratory Cough Sub-study Only) 68
8.1.8.3 Asthma Control Questionnaire-6 68
8.1.8.4 St George's Respiratory Questionnaire 69
8.1.8.5 Sino-nasal Outcome Test-22 69
8.1.8.6 Patient Global Impression of Benefit/Risk 70

8.1.8.7 Study Participant Feedback Questionnaire 70
8.2 Safety Assessments 70
8.2.1 Medical, Surgical, and Asthma History 70
8.2.2 Physical Examinations, Weight, and Height 70
8.2.3 Vital Signs 71
8.2.4 Electrocardiograms 71
8.2.5 Echocardiograms 72
8.2.6 SARS-CoV-2 Serology Testing 72
8.2.7 Clinical Safety Laboratory Assessments 72
8.3 Adverse Events and Serious Adverse Events 74
8.3.1 Time Period and Frequency for Collecting AE and SAE Information 74
8.3.2 Follow-up of AEs and SAEs 74
8.3.3 Causality Collection 75
8.3.4 Disease Under study 75
8.3.5 Adverse Events Based on Signs and Symptoms 75
8.3.6 Adverse Events Based on Examinations and Tests 76
8.3.7 Adverse Events of Special Interest 76
8.3.8 Hy's Law 77
8.3.9 Reporting of Serious Adverse Events 77
8.3.10 Pregnancy 77
8.3.10.1 Maternal Exposure 78
8.3.10.2 Paternal Exposure 78
8.3.11 Medication Error 78
8.4 Overdose 79
8.5 Human Biological Sample Biomarkers 79
8.5.1 Human Biological Samples 79
8.5.2 Pharmacokinetics 80
8.5.2.1 Determination of Drug Concentration 80
8.5.3 Immunogenicity Assessments 80
8.5.4 Pharmacodynamics 81
8.5.5 Collection of Mandatory Samples for Biomarker Analysis 81
8.5.6 Other study related biomarker research 82
8.6 Optional Genomics Initiative Sample 82
8.7 Health Economics 83
8.8 Impact of COVID-19 Pandemic 83
9 STATISTICAL CONSIDERATIONS 83
9.1 Statistical Hypotheses 83
9.2 Sample Size Determination 83
9.3 Populations for Analyses 84
9.4 Statistical Analyses 84
9.4.1 General Considerations 85
9.4.2 Efficacy 85
9.4.2.1 Primary Endpoint 85
9.4.2.2 Secondary and Exploratory Endpoints 85

9.4.3 Subgroup Analyses 86
9.4.4 Safety 86
9.4.5 Other Analyses 86
9.4.5.1 Immunogenicity and PK 86
9.4.5.2 Exploratory Biomarker Outcomes 87
9.4.5.3 Exploratory Analyses 87
9.5 Interim Analyses 87
9.6 Data Monitoring Committee 87
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 88
11 REFERENCES 131

LIST OF FIGURES

Figure 1 Study Flow Diagram 14
Figure 2 Reversibility algorithm 62

LIST OF TABLES

Table 1 Schedule of Activities: Screening Period 15
Table 2 Schedule of Activities: Study Intervention and Follow-up Periods 18
Table 3 Risk Assessment 25
Table 4 Objectives and Endpoints 32
Table 5 Study Interventions 50
Table 6 Study Intervention Dose Preparation 52
Table 7 Laboratory Safety Variables 73
Table 8 Populations for Analysis 84
Table I9 Highly Effective Methods of Contraception 113

LIST OF APPENDICES

Appendix A Regulatory, Ethical, and Study Oversight Considerations 89
Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 93
Appendix C Handling of Human Biological Samples 98
Appendix D Optional Genomics Initiative Sample 100

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law 103
Appendix F Maintenance Therapy Equivalence Table 108
Appendix G National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis 109
Appendix H Signs, Symptoms, and Management of Acute Anaphylaxis 110
Appendix I Contraception Guide 113
Appendix J Abbreviations 114
Appendix K Protocol Amendment History 118

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase II, Randomised, Double-blind, Placebo-controlled Study to Assess the Efficacy and Safety of MEDI3506 in Adult Participants with Uncontrolled Moderate-to-severe Asthma

Short Title: Study to Assess the Efficacy and Safety of Subcutaneously Injected MEDI3506 in Adults with Uncontrolled Moderate-to-severe Asthma

Rationale:

The MEDI3506 pre-clinical profile suggests that MEDI3506 can reduce asthmatic airway inflammation, improve epithelial integrity, reduce mucus production, and improve muco-ciliary transport. As such, MEDI3506 is hypothesised to impact asthma disease status by increasing forced expiratory volume in the first second (FEV_1, and other physiological measures of lung function) and reducing frequency and severity of asthma exacerbations, thereby improving quality of life. This Phase II study aims to assess the efficacy and safety of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.

Objectives and Endpoints

Objective	Endpoint
Primary	
To assess the effect of MEDI3506 compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	As measured in clinic, change from baseline to Week 16 in pre-BD FEV_1 (L).
Secondary	
To further assess the effect of MEDI3506 compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	As measured in clinic, change from baseline to Weeks 8 and 16 in post-BD FEV_1 (L).
To assess the PK of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.	Serum MEDI3506 concentration-time profiles during the intervention and follow-up periods.
To assess the immunogenicity of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.	ADA during the intervention and follow-up periods.
To assess the effect of MEDI3506 compared with placebo on asthma control in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Week 16 in ACQ-6 score. Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16. Proportion of participants achieving ACQ-6 well controlled status (defined as ACQ-6 score ≤ 0.75 at Week 16).

Objective	Endpoint
To assess the effect of MEDI3506 compared with placebo on health status in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Week 16 in SGRQ score. Proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16.
To assess the effect of MEDI3506 compared with placebo on CompEx in adult participants with uncontrolled moderate-to-severe asthma.	Time to first CompEx event based on the period from baseline to Week 16. CompEx annualised event rate.
To assess the effect of MEDI3506 compared with placebo on concentration of FeNO in adult participants with uncontrolled moderate-to-severe asthma.	Percent change from baseline to Week 16 in concentration of FeNO in exhaled breath.

ACQ-6 = asthma control questionnaire-6; ADA = anti-drug antibody(ies); BD = bronchodilator; CompEx = composite endpoint for severe exacerbations of asthma; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in the first second; L = litre(s); PK = pharmacokinetics; SGRQ = St George's respiratory questionnaire.

For safety and exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

Study D9181C00001 is a Phase II, randomised, double-blind, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, pharmacokinetics (PK) and immunogenicity of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma on standard of care (SOC). The study has 3 treatment-arms. Participants who fail screening can be re-screened.

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

Number of Participants:

Approximately 228 participants will be randomised to achieve 216 evaluable participants.

Intervention Groups and Duration:

Participants will be randomised in a 1:1:1 ratio to receive CCI mg MEDI3506, CCI mg MEDI3506, or placebo every CCI by subcutaneous (SC) injection for a total of CCI doses.

Participants will be enrolled in this study for up to 29 weeks. The study comprises of 3 periods including the screening period of up to 5 weeks, an intervention period of 16 weeks, and a follow-up period of 8 weeks.

Data Monitoring Committee:

A Data Safety Monitoring Board (DSMB) has been established to oversee the MEDI3506 clinical development programme. 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.

Statistical Methods

A sample size of 216 participants (72 participants per treatment group), randomised 1:1:1 to MEDI3506 CCI mg: MEDI3506 CCI mg: placebo, will provide at least 80% power to detect a statistically significant difference in change from baseline to Week 16 in pre-bronchodilator (BD) FEV_1, assuming a difference of 150 mL between placebo and MEDI3506, a between-participant standard deviation (SD) of 420 mL and a one-sided-10% alpha level. To allow for 5% participants being ineligible for the primary analysis, a total of approximately 228 participants will be randomised (approximately 76/arm).

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 16 (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 16, irrespective of whether the participant discontinued study intervention or received rescue therapy.

A similar approach will be taken for the analysis of asthma control questionnaire-6 (ACQ-6), St George's respiratory questionnaire (SGRQ), and fractional exhaled nitric oxide (FeNO). The difference in mean change from baseline in post-BD FEV_1 at Weeks 8 and 16 will be estimated using a repeated measures mixed effects analysis of covariance model, similar to that described for the primary efficacy analysis. Data may be log-transformed prior to analysis where appropriate. Time to first composite endpoint for severe exacerbations of asthma (CompEx) event will be analysed using a Cox proportional hazard model, with treatment fitted as a covariate.

MEDI3506 serum concentrations will be tabulated along with descriptive statistics. Mean and individual serum MEDI3506 concentration-time profiles will be plotted. Population PK modelling may be performed if data allow. Positive antibodies to MEDI3506 will be reported by treatment group. If there is a high incidence of anti-drug antibody (ADA), the association of ADA with MEDI3506 concentration will be assessed.

1.2 Schema

The general study design is summarised in Figure 1.

CCI [redacted]

CCI [redacted]

[redacted]

1.3 Schedule of Activities

Once informed consent has been obtained, eDiary provision and training for site and home visits should occur first during SV1, followed by patient reported outcome (PRO) assessments. PRO assessments should be conducted first at all other visits. For all participants, in-clinic spirometry testing must be initiated between 6:00 AM and 11:00 AM during the screening or re-screening period, and randomisation visit (SV4). Whenever electrocardiograms (ECGs), vital signs, 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. Whenever FeNO, airwave oscillometry (AO), and spirometry are scheduled for the same nominal time, the order should be as follows: FeNO, AO, then spirometry. Nasal sampling should be performed last, with nasal lining fluid collection performed before nasal epithelium collection (when both are scheduled). Urine samples may be collected at any time during the study visit (when scheduled). On days when investigational product is administered, all assessments should be performed pre-dose unless otherwise specified in the Schedule of Activities. Refer to Section 8 for additional information on assessment ordering (eg, pre-, post-dose or multiple timepoints within a visit). In the event that a clinical laboratory test result is not available from central laboratories during the screening period, see Section 8.2.7.

Table 1 Schedule of Activities: Screening Period

Visit Number	**SV1**	**SV2**	**SV3**
Procedure/Study Day	**-35 to -28**	**-14 to -6**	**Visit no longer needed**
Study Week	**-4**	**-1**	
Written ICF CCI [redacted] /assignment of SID number	X [a]		
Written informed consent for future use and/or DNA analysis (optional)	X		
Verify eligibility criteria	X	X	
Demographics	X		
Baseline asthma assessments			
Provision of, and training on use of, home spirometry device and eDiary	X		
ACQ-6	X	X	
SGRQ		X	
SNOT-22 (comorbid CRS participants only)	X		
At-home eDiary completion and spirometry use	Twice daily throughout screening period		

Table 1 Schedule of Activities: Screening Period

Visit Number	SV1	SV2	SV3
Procedure/Study Day	**-35 to -28**	**-14 to -6**	**Visit no longer needed**
Study Week	**-4**	**-1**	
Assess adherence to at-home eDiary completion, spirometry, and SOC medication use		X	
Assessment of asthma exacerbations		X	
FeNO	X	X	
Airwave oscillometry		X	
In-clinic spirometry (pre-BD)	X	X	
In-clinic spirometry (post-BD)	X [b]	X [c]	
Safety assessments			
Concomitant medications	X	X	
Medical, surgical, and asthma history	X		
Physical examination (complete)	X		
Weight and height	X		
Vital signs	X		
ECG	X		
Echocardiogram		X [d]	
SARS-CoV-2 PCR test	X [e]	X [f]	
Assessment of AEs/SAEs	X	X	
Collect blood for:			
Haematology	X		
Coagulation parameters	X		
Serum chemistry	X		
Serum pregnancy test [g]	X		
FSH (if needed to confirm post-menopausal status in female participants aged < 50 years and not on HRT)	X		
HbA1c	X		
Hepatitis B (HBsAg, anti-HBs, anti-HBc), and C; HIV-1 and HIV-2	X		
IGRA (TB test) [h]	X		
NT-proBNP	X		
Exploratory biomarkers (serum)	X		
Total IgE (serum)	X		
EDN (plasma)	X		

Table 1 Schedule of Activities: Screening Period

Visit Number	SV1	SV2	SV3
Procedure/Study Day	**-35 to -28**	**-14 to -6**	**Visit no longer needed**
Study Week	**-4**	**-1**	
Collect urine for:			
Urinalysis	X		
Urine pregnancy test [g]		X	
Pandemic impact assessment		X	
Exploratory cough sub-study only			
At-home cough monitoring (for the 24 hours post-clinic visit)		X	
Cough VAS		X	

[a] ICF may be signed prior to SV1, providing all screening visits are scheduled to take place within a 28 to 35 day timeframe.
[b] Post-BD spirometry should be performed at SV1 if documented evidence of asthma (see Section 5.1) is not already available.
[c] Post-BD spirometry should be performed at SV2 if documented evidence of asthma (see Section 5.1) is not already available.
[d] May be performed any time after signing of informed consent, so that results are available prior to SV4 (randomisation).
[e] Participants are permitted to continue screening if the result from the SARS-CoV-2 PCR test performed at SV1 has not been returned by SV2.
[f] Test may be performed at either visit or anytime on or after Day -7 such that the results are available prior to SV4 (see Exclusion Criterion 1).
[g] Female participants of childbearing potential only.
[h] See Exclusion Criterion 4.

ACQ-6 = asthma control questionnaire-6; AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; BD = bronchodilator; CRS = chronic rhinosinusitis; ECG = electrocardiogram; EDN = eosinophil derived neurotoxin; FeNO = fractional exhaled nitric oxide; FSH = follicle-stimulating hormone; HbA1c = haemoglobin A1c; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; HRT = hormone replacement therapy; ICF = informed consent form; IgE = immunoglobulin E; IGRA = interferon gamma release assay; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St George's respiratory questionnaire; SID = subject identification; SNOT-22 = sino-nasal outcome test-22; CCI [redacted] SOC = standard of care; SV = study visit; TB = tuberculosis; VAS = visual analogue scale.

Table 2 Schedule of Activities: Study Intervention and Follow-up Periods

Period	**Study Intervention**							**Follow-up**		
Visit Number	**SV4 (Random-isation)**	**SV5 (TC)**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**E/D**
Study Day	**1**	**2**	**8 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**113 (± 3)**	**141 (± 3)**	**169 (± 3)**	
Study Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	
Efficacy assessments										
ACQ-6	X		X	X	X	X	X		X	X
SGRQ	X			X		X	X		X	X
SNOT-22 (comorbid CRS participants only)	X		X	X	X	X	X			
At-home eDiary completion and spirometry use	Twice daily throughout the intervention period.									
Assess adherence to at-home eDiary completion, spirometry, and SOC medication use	X	X	X	X	X	X	X	X	X	
Assessment of asthma exacerbations	X	X	X	X	X	X	X	X	X	X
PGI-BR							X			
Study participant feedback questionnaire (optional)	X						X		X	X
FeNO	X		X	X	X	X	X	X	X	X
Airwave oscillometry (pre-administration of study intervention)	X		X	X	X	X	X			
Airwave oscillometry (4 hours post-administration of study intervention)	X [a]									

Table 2 Schedule of Activities: Study Intervention and Follow-up Periods

Period	Study Intervention							Follow-up		
Visit Number	**SV4 (Random-isation)**	**SV5 (TC)**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**E/D**
Study Day	**1**	**2**	**8 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**113 (± 3)**	**141 (± 3)**	**169 (± 3)**	
Study Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	
In-clinic spirometry (pre-BD) (pre-administration of study intervention)	X		X	X	X	X	X	X	X	X
In-clinic spirometry (4 hours post-administration of study intervention)	X [a]									
In-clinic spirometry (post-BD)	X				X		X			
Safety assessments										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination	X [b]		X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [c]	X [c]
Weight	X						X		X	X
Vital signs	X		X	X	X	X	X	X	X	X
ECG	X [d]						X		X	X
Echocardiogram [e]						X [f]				
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X
Injection site reactions	X		X	X	X	X	X			X
SARS-CoV-2 PCR test [g]	X		X	X	X	X	X	X	X	X
Collect blood [h] for:										
Haematology	X		X	X	X	X	X		X	X
Coagulation parameters	X		X	X	X	X	X		X	X
Serum chemistry	X		X	X	X	X	X		X	X

Table 2 Schedule of Activities: Study Intervention and Follow-up Periods

Period	Study Intervention							Follow-up		
Visit Number	**SV4 (Random-isation)**	**SV5 (TC)**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**E/D**
Study Day	**1**	**2**	**8 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**113 (± 3)**	**141 (± 3)**	**169 (± 3)**	
Study Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	
NT-proBNP [e]					X	X	X		X	X
PK (serum)	X		X	X	X	X	X	X	X	X
Immunogenicity (serum)	X		X	X	X	X	X		X	X
Exploratory biomarkers (serum)	X		X	X	X	X	X	X	X	X
SARS-CoV-2 serology test (serum)	X						X			X
Total IgE (serum)	X						X		X	
Allergen-specific IgE (serum)	X									
EDN (plasma)	X			X			X		X	
sST2 (serum)	X						X			
RNA PAXgene	X						X			
CCI [redacted]	CCI [redacted]									
CCI [redacted]	CCI [redacted]									
DNA for exploratory genetics evaluation (optional)	X [i]									
Collect urine for:										
Urinalysis	X		X	X	X	X	X			X
Pregnancy test [j]	X			X	X	X	X		X	X

Table 2 Schedule of Activities: Study Intervention and Follow-up Periods

Period	Study Intervention							Follow-up		
Visit Number	**SV4 (Random-isation)**	**SV5 (TC)**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**E/D**
Study Day	**1**	**2**	**8 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**113 (± 3)**	**141 (± 3)**	**169 (± 3)**	
Study Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	
Collect nasal sample for:										
Nasal mucosal sampling (lining fluid)	X			X	X	X	X	X	X	
Nasal mucosal sampling (mRNA) [k]	X						X			
Verify eligibility criteria	X									
Randomisation	X									
Study intervention administration [l]	[redacted]			[redacted]	[redacted]	[redacted]				
Pandemic impact assessment [m]	X	X	X	X	X	X	**X**	**X**	**X**	**X**
Exploratory cough sub-study only										
At-home cough monitoring (for the 24 hours post-clinic visit)							X			
Cough VAS							X			

[a] Airway oscillometry and spirometry performed 4 hours (± 15 minutes) post administration of study intervention will require 4 hours withhold of bronchodilator (see Section 6.5.3).
[b] Brief physical examination.
[c] Complete physical examination.
[d] Triplicate ECG. The mean value of each parameter from the triplicate will be used as the baseline value.
[e] Echocardiogram and NT-proBNP assessments also to be performed as required, for participants who might be experiencing heart failure, or as soon as possible after heart failure might have occurred.
[f] May be performed at any time at or between SV9 (Week 12) and SV10 (Week 16) inclusive.
[g] Testing may be performed at any point for a participant suspected of having COVID-19.
[h] Prior to administration of study intervention on days when study intervention is administered.

Table 2 Schedule of Activities: Study Intervention and Follow-up Periods

Period	Study Intervention							Follow-up		
Visit Number	**SV4 (Random-isation)**	**SV5 (TC)**	**SV6**	**SV7**	**SV8**	**SV9**	**SV10**	**SV11**	**SV12**	**E/D**
Study Day	**1**	**2**	**8 (± 3)**	**29 (± 3)**	**57 (± 3)**	**85 (± 3)**	**113 (± 3)**	**141 (± 3)**	**169 (± 3)**	
Study Week	**0**	**0**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	

[i] If not performed at SV4, can be performed at any subsequent visit. As a last resort if the participant has completed the study (and not withdrawn consent) but the sample has not been received by the analysing laboratory, the site should ask the participant if he/she would be willing to attend an additional optional visit to provide this sample.

[j] Female participants of childbearing potential only.

[k] If deemed by investigator to be intolerable for individual participant at SV4 (eg, due to nasal polyps), subsequent assessments may be omitted. If this assessment is not performed at SV4 for any reason, it should not be repeated at SV10.

[l] Participants should be monitored for a minimum of one to 2 hours after administration of study intervention (see Section 8.2.3). 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. Additional details on anaphylactic reactions are provided in Appendix G and Appendix H.

[m] For COVID-19 mitigation, please see Section 2.3.1.2.

ACQ-6 = asthma control questionnaire-6; AE = adverse event; BD = bronchodilator; COVID-19 = coronavirus disease 2019; CRS = chronic rhinosinusitis; E/D = early study intervention discontinuation; ECG = electrocardiogram; EDN = eosinophil derived neurotoxin; FeNO = fractional exhaled nitric oxide; IgE = immunoglobulin E; IL = interleukin; mRNA = messenger RNA; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; PGI-BR = patient global impression of benefit/risk; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St George's respiratory questionnaire; SNOT-22 = sino-nasal outcome test-22; CCI [redacted] SOC = standard of care; sST2 = soluble ST2; SV = study visit; TC = telephone contact; VAS = visual analogue scale.

2 INTRODUCTION

MEDI3506 is a human IgG1 mAb that binds to human IL-33. MEDI3506 binds full length and mature forms of human IL-33 with exceptionally high affinity and prevents IL-33 binding to soluble (sST2) and membrane-bound forms of ST2 (also known as IL-1RL1) receptor. Several clinical and non-clinical studies point to the IL-33/ST2 signalling axis playing a key role in the pathogenesis of asthma. Thus, blocking this signalling pathway could be of therapeutic benefit in asthma. MEDI3506 is currently in development for the treatment of asthma, AD, COPD, and DKD.

2.1 Study Rationale

The MEDI3506 pre-clinical profile suggests that MEDI3506 can reduce asthmatic airway inflammation, improve epithelial integrity, reduce mucus production, and improve muco-ciliary transport. As such, MEDI3506 is hypothesised to impact on asthma disease status by increasing FEV_1 (and other physiological measures of lung function) and reducing frequency and severity of asthma 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.

This Phase II study aims to assess the efficacy and safety of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.

2.2 Background

Asthma is a chronic inflammatory disease of the airways characterised by bronchial hyperreactivity and reversible airflow limitation. International treatment guidelines for asthma recommend ICS as first line therapy (GINA 2020). For individuals who are symptomatic on medium dose ICS monotherapy, step-up therapy with LABA is the recommended next treatment option followed by other controller therapies including leukotriene receptor antagonists, theophylline, and oral corticosteroids. ‘Biologic agents’ (eg, omalizumab and benralizumab) that inhibit specific molecular targets such as IgE or Th2 cytokines and their respective receptors are reserved for those with severe uncontrolled asthma. Furthermore, all currently approved asthma controller therapies have little or no impact on the natural history of the disease (ie, most people with moderate-severe asthma need life-long therapy). There is a clear unmet need for asthma therapies that not only better control symptoms, but lead to disease modification.

Numerous studies have shown a key role for IL-33 in asthma. The genes encoding IL-33 and ST2/IL1RL1 have been identified as major susceptibility loci for human asthma in several genome wide association studies (Bonnelykke et al 2014; Gudbjartsson et al 2009; Hirota et al 2011; Moffat et al 2010; Shrine et al 2019; Torgerson et al 2011; Wan et al 2012) and were among the few genes reproducibly found to be associated with asthma across diverse ethnic groups. In addition, a rare IL-33 loss-of-function mutation has been recently described that reduces blood eosinophil counts and protects from asthma (Smith et al 2017). The protective effect remained, although weaker, after correcting for eosinophil counts, suggesting that IL-33 may influence asthma risk in part by controlling blood eosinophil count, and also through additional biological pathways (Mousas et al 2017).

Two Phase II studies support a role for anti-IL-33 therapy in asthma treatment. In a proof-of-concept study involving adult patients with moderate-to-severe asthma, REGN3500 monotherapy (ICS and LABA maintenance therapy were withdrawn during the trial) met the primary endpoint of improvement in loss of asthma control and significantly improved lung function compared to placebo, meeting a key secondary endpoint (NCT03387852). In a separate Phase II clinical study, a single IV dose of etokimab was administered to patients with uncontrolled moderate-to-severe asthma despite being on treatment with high dose combination ICS plus LABA therapy. Compared with a placebo group, asthmatics treated with etokimab had a significant improvement in lung function (FEV_1) and a reduction in blood eosinophils (NCT03469934).

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 benefit, potential risks, and mitigation strategies of MEDI3506 may be found in the IB.

2.3.1 Risk Assessment

Potential risks for this study population, study procedures, and MEDI3506 administration and mitigation strategies are listed in Table 3. A blinded review of the safety data for AEs will be performed regularly and any potential emerging risks highlighted to the DSMB for further consideration.

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Study Population Related		
Worsening of asthma control	Efficacy of MEDI3506 on asthma not yet determined.	• Participants will continue on their current asthma controller and reliever treatments as required. • Participants will be treated for exacerbations of asthma if they occur. • eDiary will trigger 'worsening of asthma alerts' for participants and research sites.
Study Procedure Related		
Nasal mucosal sampling (mRNA)	Temporary, minor discomfort (similar to drawing blood).	• To be performed by appropriately trained staff using appropriate personal protective equipment. • If deemed by investigator to be intolerable for individual participant at SV4 (eg, due to nasal polyps), subsequent assessments may be omitted (see Table 2).
MEDI3506/Study Intervention Related		
Gastrointestinal adverse reactions.	Observation of what was considered an incidental finding of ulcerative colitis in a 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 (see IB Section 5.5.1.1).	Exclusion of individuals with history of ulcerative colitis, Crohn's disease, or microscopic colitis diagnosed by either gastroenterologist or by histopathology (see Section 5.2).
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; see IB Section 5.5.2.1).	Exclusion of individuals with active infection and/or latent infections or individuals who are immunosuppressed/compromised (see Section 5.2).

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Progression of heart failure.	CCI [redacted]	• Exclusion of individuals at risk of developing of heart failure (see Section 5.2). • Exclusion of individuals with LVEF < 45% (see Section 5.2). • Monitoring of study participants with echocardiograms and NT-proBNP (see Table 2).
Injection site reactions.	This is based on the SC route of administration and the nature of MEDI3506 as an exogenous protein substance (see IB Section 5.5.3.1).	• Instructions on injection technique including rotation of injection sites (see Section 6.2.2.1). • Routine monitoring for injection site reactions will be undertaken at each SV (see Table 2).
Serious hypersensitivity (including Type I to IV hypersensitivity reactions) and immune complex disease.	As mAb 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 ADA could result in immune complex disease (see IB Section 5.5.4.1).	• Exclude individuals with a known history of allergy or severe reaction to: ° Any component of the study intervention. ° Biologic agents. ° Human gamma globulin therapy formulations (see Section 5.2). • Exclude individuals with hereditary fructose intolerance (see Section 5.2). • Required monitoring of participants for a minimum of one to 2 hours after administration of study intervention (see Table 2). • Sites must be equipped to diagnose and manage anaphylaxis and serious allergic reactions until the participant can be transferred to a suitable facility (see Table 2 and Appendix H). • Serum tryptase will be determined in the event of suspected anaphylactic symptoms (see Table 2 and Appendix H).

Table 3 Risk Assessment

Potential Risk of Clinical Significance	Rationale for Risk	Mitigation Strategy
Reproductive toxicity.	Consistent with ICH guidance on the timing of nonclinical studies, MEDI3506 has not been evaluated in embryo-foetal development toxicity studies (see IB Section 5.5.5.1).	• Stipulation of highly effective contraceptive requirements for participants (see Appendix I). • Female participants may only be included if they have a negative pregnancy test during screening and prior to administration of study intervention, and agree to use a highly effective method of contraception from screening until the end of the study (see Section 5.1). • Male participants may only be included if they agree to use a male condom with (if available) spermicide and another highly effective method of contraception during the intervention and follow-up periods (see Section 5.1).

ADA = anti-drug antibody(ies); IB = Investigator's Brochure; ICH = International Council for Harmonisation; IL = interleukin; LVEF = left ventricular ejection fraction; mAb= monoclonal antibody(ies); mRNA = messenger RNA; NT-proBNP = N-terminal prohormone of B-type natriuretic peptide; SC = subcutaneous; sST2 = soluble ST2; SV = study visit.

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 coronavirus disease 2019 (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).

2.3.1.1 Study Conduct During COVID-19 Pandemic

Coronavirus disease 2019 (COVID-19) 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. Specifically, this study would not be initiated in regions where local and/or national authorities have issued stay-in-place or lock-down orders. Hence, AstraZeneca will commence this study when local and national governments indicate that it is acceptable to perform clinical studies. Furthermore, each study site must have appropriate measures to ensure safety of site staff and participants, and this study would be paused if local or national governments or sites determine that they can no longer support safe conduct of clinical research. 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 and the safety of site staff and participants can be ensured.

If during study conduct, local or national governments or sites determine that the current environment can no longer support safe conduct of clinical research, this study would be paused.

2.3.1.2 COVID-19 Mitigations

In order to exclude higher risk participants, the age range is set at 18 to < 65 years inclusive at time of enrolment.

Severe asthma is 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.
   (a) Participants with history of COVID-19 pneumonia diagnosed based on radiological assessment.
   (b) Participants with history of COVID-19 and significant findings from pulmonary imaging tests.

(c) Participants with history of COVID-19 requiring hospitalisation and/or oxygen supplementation therapy.

Because the run-in period ranges from 28-35 days, participants will be tested for active SARS-CoV-2 infection using a PCR test targeting SARS-CoV-2 at 2 screening visits (see SOA; see Table 1, Section 1.3), and those with a positive result prior to randomisation will become screen failures.

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.

Investigators should ensure that potential participants with significant risk factors for COVID-19 related complications are not enrolled as per Exclusion Criterion 13 (Section 5.2).

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. 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 analysed using a repeated measures mixed effect model which, in the event of missing data, uses all data that are available. The sponsor will monitor the number of discontinuations, withdrawals, missed visits and other missing data.

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 focus, in part, on AEs associated with new onset SARS-CoV-2 infection and participants withdrawn due to COVID-19 illness.

All site staff should wear personal protective equipment in accordance with local or national guidelines.

If, for reasons related to the COVID-19 pandemic, a participant is not able to attend their scheduled visit with in 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 if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow collection of data for AEs, concomitant medications, adherence to the eDiary and PRO measures to be reported and documented. The term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

2.3.1.3 Vaccination Against COVID-19

There are 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 minimised.

To help ensure the interpretability of safety data, receipt of COVID-19 vaccine (either first or subsequent dose) is prohibited within 30 days before randomisation or within 7 days before or after any dose of study intervention (Section 6.5.4). Receipt of, at least, the first dose of COVID-19 vaccine more than 30 days before randomisation, 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 study intervention. If the (approximate) date of a subsequent dose of COVID-19 vaccination is known, then enrolment of the participant should be timed so that the dose is not within 30 days prior to scheduled randomisation. If this date is not known then enrolment into the study should not be delayed. If an enrolled participant does (unexpectedly) receive COVID-19 vaccine within 30 days prior to scheduled randomisation, the site should contact the AstraZeneca Study Physician for advice on how the situation should be managed.

2.3.2 Benefit Assessment

The purpose of this Phase II, proof-of-concept clinical study is to evaluate the efficacy and safety of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma. For participants randomised to MEDI3506, there is a potential benefit in terms of improvement of their asthma status. However, the efficacy of MEDI3506 in participants with asthma is yet to be determined. Participants may derive benefit from health assessments (eg, ECG, echocardiogram, clinical laboratory safety measurements, and SOC adherence monitoring) performed as part of the study.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures to minimise risk to participants in this study, the potential risks in association with MEDI3506 are justified by the potential benefit in terms of improvement of their asthma status.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints

Objective	Endpoint
Primary	
To assess the effect of MEDI3506 compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	As measured in clinic, change from baseline to Week 16 in pre-BD FEV_1 (L).
Secondary	
To further assess the effect of MEDI3506 compared with placebo on lung function, in adult participants with uncontrolled moderate-to-severe asthma.	As measured in clinic, change from baseline to Weeks 8 and 16 in post-BD FEV_1 (L).
To assess the PK of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.	Serum MEDI3506 concentration-time profiles during the intervention and follow-up periods.
To assess the immunogenicity of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.	ADA during the intervention and follow-up periods.
To assess the effect of MEDI3506 compared with placebo on asthma control in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Week 16 in ACQ-6 score. Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16. Proportion of participants achieving ACQ-6 well controlled status (defined as ACQ-6 score ≤ 0.75 at Week 16).
To assess the effect of MEDI3506 compared with placebo on health status in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Week 16 in SGRQ score. Proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16.
To assess the effect of MEDI3506 compared with placebo on CompEx in adult participants with uncontrolled moderate-to-severe asthma.	Time to first CompEx event based on the period from baseline to Week 16. CompEx annualised event rate.
To assess the effect of MEDI3506 compared with placebo on concentration of FeNO in adult participants with uncontrolled moderate-to-severe asthma.	Percent change from baseline to Week 16 in concentration of FeNO in exhaled breath.

Table 4 Objectives and Endpoints

Objective	Endpoint
Safety	
To assess the safety and tolerability of MEDI3506 compared with placebo, in adult participants with uncontrolled moderate-to-severe asthma.	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 • Number of participants seropositive for SARS-CoV-2 at end of study who were seronegative at randomisation visit • For participants testing positive for SARS-CoV-2 (by PCR or serology test), during the intervention and follow-up periods, the number and proportion of patients with COVID-19 AEs/SAEs and the proportion asymptomatic.
Exploratory	
To further assess the longitudinal effect of MEDI3506 compared with placebo on lung function in adult participants with uncontrolled moderate-to-severe asthma.	As measured at home, change from baseline up to Week 24 in 2-weekly mean PEF and FEV_1
To assess the effect of MEDI3506 compared with placebo on airway hyperresponsiveness in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Weeks 8 and 16 in FEV_1% reversibility.
To assess the effect of MEDI3506 compared with placebo on asthma related inflammatory blood biomarkers in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Weeks 1, 4, 8, 12, 16, 20 and 24 in inflammatory blood biomarker levels, including but not limited to: • CCI [redacted] • Serum IL-5. • Serum IL-13. • Serum TSLP. Change from baseline to Weeks 4, 16, and 24 in plasma EDN. Change from baseline to Weeks 16 and 24 in total IgE. Change from baseline to Week 16 in: • sST2. • Proinflammatory gene signatures in whole blood.

Table 4 Objectives and Endpoints

Objective	Endpoint
To assess the longitudinal effect of MEDI3506 compared with placebo on small airway function in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Weeks 1, 4, 8, 12, and 16 in airway reactance and resistance as assessed by AO parameters, including but not limited to: • R5 • R20 • R5-R20 • AX
To assess the longitudinal effect of MEDI3506 compared with placebo on lung function in adult participants with uncontrolled moderate-to-severe asthma.	As measured in clinic, change from baseline in pre-BD FEV1 to Weeks 1, 4, 8, 12, 20, and 24.
To assess the acute effect of MEDI3506 compared with placebo on pre-BD FEV1 in adult participants with uncontrolled moderate-to-severe asthma.	As measured in clinic, change in pre-BD FEV1 (L) from pre-administration of study intervention to 4 hours post-administration of MEDI3506 or placebo at Day 1.
To assess the effect of MEDI3506 compared with placebo on asthma control in adult participants with uncontrolled moderate-to-severe asthma.	During the intervention period (baseline to Week 16): • Annualised rate of asthma exacerbations. • Annualised rate of hospitalised asthma exacerbations.
To assess the longitudinal effect of MEDI3506 compared with placebo on asthma control and health status in adult participants with uncontrolled moderate-to-severe asthma.	Change from baseline to Weeks 1, 4, 8, 12, and 24 in ACQ-6 score. Change from baseline to Weeks 4, 12, and 24 in SGRQ score. Change from baseline up to Week 24 in 2-weekly mean daily rescue medication usage (puffs/day). Change from baseline to Weeks 4, 8, 12, 16, 20, and 24 in: • Asthma symptom score. • Mean number of night-time awakenings.
To assess the benefit-risk profile of MEDI3506 as perceived by adult participants with uncontrolled moderate-to-severe asthma.	PGI-BR at Week 16.
To evaluate CCI and inflammatory blood biomarkers that may predict an efficacy response to MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma.	CCI Association of allergen-specific IgE status with primary and secondary efficacy endpoints at Week 16.
To assess the effect of MEDI3506 compared with placebo on asthma related inflammatory airway biomarkers in adult participants with uncontrolled moderate-to-severe asthma.	Percent change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 in concentration of FeNO. Change from baseline to Weeks 4, 8, 12, 16, 20, and 24 in exploratory biomarkers measured in nasal lining fluid. Change from baseline to Week 16 in mRNA nasal transcriptome.

Table 4 Objectives and Endpoints

Objective	Endpoint
To assess the effect of MEDI3506 compared with placebo on nasal symptom control in a subset of adult participants with uncontrolled moderate-to-severe asthma who have comorbid CRS.	Change from baseline to Weeks 1, 4, 8, 12, and 16 in SNOT-22 score.
Exploratory cough sub-study	
To evaluate the effect of MEDI3506 compared with placebo on objective cough measures in adult participants with uncontrolled moderate-to-severe asthma	Change from baseline to Week 16 in: • Daily (ie, 24 hour) cough frequency. • Awake time cough frequency. • Night-time cough frequency. • Cough VAS.

ACQ-6 = asthma control questionnaire-6; ADA = anti-drug antibody(ies); AE = adverse event; AESI = adverse event of special interest; AO = airwave oscillometry; BD = bronchodilator; COVID-19 = coronavirus disease 2019; CompEx = composite endpoint for severe exacerbations of asthma; CRS = chronic rhinosinusitis; ECG = electrocardiogram; EDN = eosinophil derived neurotoxin; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in the first second; IgE = immunoglobulin E; IL = interleukin; L = litre(s); LVEF = left ventricular ejection fraction; mRNA = messenger RNA; NT-proBNP = N-terminal prohormone of B-type natriuretic hormone; PCR = polymerase chain reaction; PEF = peak expiratory flow; PGI-BR = patient global impression of benefit/risk; PK = pharmacokinetic(s); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SGRQ = St George's respiratory questionnaire; SNOT-22 = sino-nasal outcome test-22; CCI sST2 = soluble ST2; TSLP = thymic stromal lymphopoietin; VAS = visual analogue scale.

4 STUDY DESIGN

4.1 Overall Design

Study D9181C00001 is a Phase II, randomised, double-blind, placebo-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, PK and immunogenicity of MEDI3506 in adult participants with uncontrolled moderate-to-severe asthma on SOC.

Approximately 228 participants will be randomised in a 1:1:1 ratio to achieve 216 evaluable participants. Participants will receive CCI mg MEDI3506, CCI mg MEDI3506, or placebo CCI by SC injection for a total of C doses. The randomisation will be stratified according to cough sub-study participation. Note that the exploratory cough sub-study may not be activated in all countries.

Participants who fail screening can be re-screened.

Participants will be enrolled in this study for up to 29 weeks. The study comprises of 3 periods including the screening period of up to 5 weeks, an intervention period of 16 weeks, and a follow-up period of 8 weeks.

Safety data from this study will be provided to the MEDI3506 DSMB (see Appendix A 4).

Screening Period

- Participants will sign ICF and be assessed for study eligibility at SV1 (Sections 5.1 and 5.2).
- Participants assessed to have uncontrolled asthma at SV1 will undergo further baseline assessments at SV1 (see Table 1). Participants will then record adherence to their SOC asthma controller and reliever medication for a minimum period of 14 days before returning for SV2.
- At SV2, participants whose asthma remains uncontrolled despite acceptable adherence to asthma controller medication (≥ 70% adherence [days] to controller medication documented in eDiary and ACQ-6 ≥ 1.5) will undergo further screening assessments (including echocardiogram). Participants who continue to meet all eligibility criteria will be asked to attend SV4 (randomisation) 6 to 14 days following SV2.
  - A subset of participants (up to n = 60, see Section 9.2 for details) who have provided optional informed consent to participate in the sub-study, will also undergo 24-hour objective cough monitoring at home, as part of an exploratory cough sub-study, commencing at SV2 and again at SV10.

Intervention Period

- Participants will be randomised at SV4 (Day 1).
- Study interventions will be administered CCI at CCI [redacted], as well as the final dose administered at CCI [redacted]
- The primary endpoint will occur at SV10 (Week 16 post initial dose of study intervention).
- During the intervention period, participants will be required to take their asthma controller therapy regularly, complete the eDiary and perform lung function tests using a spirometry device at home regularly.
- An automated alert to the participant and site will be triggered if there is a clinically significant deterioration in any of the eDiary data points (as defined in Section 8.1.5) for > 2 days, prompting the participant to contact the investigator for further assessment of a possible asthma exacerbation. Alerts will only be received by site when eDiary uploads/syncs on adequate mobile or broadband signal; therefore, participants may initiate contact with the investigator for assessment of possible exacerbation regardless of any prompts from the site, or the eDiary and spirometry.

Follow-up Period

- Participants who complete the 16-week intervention period visit will complete an 8-week post-treatment follow-up period.
- Participants will be required to take their SOC asthma controller medications throughout the follow-up period.

4.2 Scientific Rationale for Study Design

Interleukin-33, an 'alarmin' cytokine, is expressed by epithelial and endothelial cells. Its cognate receptor, ST2, is expressed by several cell types including ILC2s, Th2 cells, Th1 cells, regulatory T cells, and mast cells. IL-33 release in airways is triggered by airway epithelial cell injury resulting from environmental factors such as airborne allergens (Cayrol and Girard 2018; Scott et al 2018), cigarette smoke (Weng et al 2018) and respiratory tract viruses (Kearley et al 2015).

Interleukin-33 stimulates ILC2s, mast cells and other airway cells to generate a variety of soluble pro-inflammatory mediators such as IL-4, IL-5, and IL-13. In turn, these mediators amplify the pro-inflammatory effects of IL-33 by recruiting immune cells, including eosinophils, into airways. In asthma, airway inflammation is causative in manifestation of symptoms and damage to structural cells. This inflammation indirectly also causes mal-adaptive epithelial repair and airway wall re-modelling / thickening of the airway wall; characteristic features of severe asthma. The functional consequences of airway wall inflammation and thickening in asthma are reduced lung function (FEV_1) and increased sensitivity to bronchoconstrictor agents such as methacholine ie, bronchial hyperreactivity. Thus, evidence suggests that IL-33 initiates and drives the cardinal features linked to the development and persistence of asthma. Consequently, neutralising IL-33 activity in asthmatic airways, would be expected to improve lung function, reduce airwall thickening and reduce bronchial hyperreactivity.

Data from large-scale genome-wide association studies strongly associate the IL-33 gene locus and the ST2 gene locus with increased risk of asthma (Bonnelykke et al 2014; Gudbjartsson et al 2009; Hirota et al 2011; Moffat et al 2010; Torgerson et al 2011; Wan et al 2012). Furthermore, one SNP in the IL-33 gene has been shown to generate a truncated, non-functional IL-33 protein. The pleiotropic pro-inflammatory effects of IL-33 in airways in conjunction with the genetic linkage to asthma risk provide strong evidence that neutralisation of IL-33 signalling may have significant therapeutic benefit in asthma. However, since asthma is a heterogeneous disease, it is not clear whether all asthmatics will benefit equally from anti-IL-33 therapy. In particular, individuals whose asthma develops early in life (< 25 years of age) are more likely to have family members with asthma ie, have a 'heritable' form of asthma, and so more likely to have IL-33 mediated disease.

This Phase II proof-of-concept study will evaluate the efficacy and safety of MEDI3506 in patients with persistent moderate-to-severe asthma inadequately controlled on ICS plus LABAs. To explore whether IL-33 variants predict response to MEDI3506, this study will test the effects of anti-IL-33 therapy in adults whose asthma developed before the age of 25 years.

4.2.1 Rationale for Endpoints

4.2.1.1 Primary Endpoints

The primary endpoint is absolute change in pre-BD FEV_1. Pre-BD FEV_1 is a valid and reliable quantitative tool to assess changes in airway obstruction in asthma over time.

4.2.1.2 Secondary and Safety Endpoints

Safety, PK, and immunogenicity endpoints will be evaluated to inform risk-benefit analyses and determine optimal dosing regimen for MEDI3506 in asthma. PROs (ACQ-6 and SGRQ) reliably identify participants with uncontrolled asthma. CompEx is a composite score of asthma control composed of data gathered using an eDiary and asthma exacerbation reporting that has predictive value in assessing whether an intervention reduces asthma exacerbations of asthma (Fuhlbrigge et al 2017). FeNO is a reliable quantitative tool to assess changes in asthma inflammation over time.

4.2.1.3 Exploratory Endpoints

Airwave oscillometry (AO) is a sensitive, non-invasive measure of airway function that concomitantly assesses peripheral (small) and central (large) airways function. FEV_1% reversibility allows for assessment of changes in irreversible airway obstruction. Although not statistically powered, asthma exacerbation rates will be captured. Blood samples will be collected from participants for the assessment of biomarkers that are relevant to asthma disease pathology and/or the mechanism of action of MEDI3506. Collection of epithelial nasal fluid and cells will be performed on participants to assess biomarkers and the mRNA nasal transcriptome, as sampling in the upper airway may provide biomarker data that are more reflective of lung pathology compared with systemic biomarkers. CCI [redacted]

Many patients with asthma have comorbid CRS. The SNOT-22, a validated questionnaire measuring nasal symptoms in participants with CRS, will be performed and evaluated in participants with comorbid CRS. Changes in SNOT-22 will be used to assess the impact of MEDI3506 on CRS.

In the exploratory cough sub-study, objective cough monitoring will assess the impact of MEDI3506 on this important symptom of asthma, related to inflammation and airway hyperresponsiveness.

4.2.2 Rationale for Study Population

Clinical efficacy of MEDI3506 has yet to be established in asthma. This study aims to determine the effects of MEDI3506 on airway function in asthmatics with uncontrolled moderate-to-severe disease receiving standard of care (see Section 5.1 for inclusion criteria). Asthmatics with early onset disease will be eligible but not those with late onset disease (onset

after age of 25 years). The early onset population of asthmatics is more likely to have IL-33 driven disease based on genome wide association study data (Gorbacheva et al 2018).

4.2.3 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 protocol to rotate injection sites (Section 6.2.2.1).
- Participant training for the eDiary and spirometry devices used at-home will be supported by trouble shooting and technical guidance (does not directly affect protocol).
- 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 protocol).
- There may be ongoing communications with participants such as newsletters and regular site contact (does not directly affect protocol).
- Site facilities were explored to support participant focused visits such as out of office or telephone contact visits (does not directly affect protocol).
- Reimbursement and travel assistance (including alternatives to the use of public transportation systems) may be considered based on site feedback (does not directly affect protocol).

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

- Text describing the order that assessments should be performed on SV days added to the schedule of activities introductory text (Section 1.3).
- Footnote ‘a’ added to the schedule of activities: screening period (Table 1) to allow flexibility for ICF to be signed at a separate, stand-alone visit in order for the participant to have sufficient time to read and absorb the study information.

4.3 Justification for Dose

The highest dose of MEDI3506 administered to participants in this study will be CCI mg by SC injection CCI. This dose is predicted to have a lower exposure, in terms of maximum concentration at steady-state ($C_{max,ss}$; approximately 2.4-fold) and AUC (approximately 1.1-fold), compared with the highest dose administered (ie, single dose of 300 mg IV MEDI3506) in the Phase I clinical study (Study D9180C00001; refer to IB for further details).

Exposures (ie, mean $C_{max,ss}$ of 1,276 µg/mL, and $AUC_{0\text{-}4\ weeks}$ at steady-state of 28,012 µg•day/mL) achieved at the 26-week NOAEL of 150 mg/kg in cynomolgus monkeys (refer to the IB for further detail) are approximately 38- and 47-fold higher than predicted at

the proposed highest dose of CCI mg SC CCI in this Phase II clinical study (refer to the IB for additional details).

The optimal serum concentration for MEDI3506 efficacy in asthma 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 mg SC CCI 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 asthma, CCI mg SC CCI is anticipated to achieve near-maximum efficacy based on the mouse and PK/PD models, and will be used in this study. The lower dose of CCI mg CCI SC will be used in this Phase II clinical study to define the efficacy of MEDI3506 at lower dose.

4.4 End of Study Definition

An individual participant will be considered to have completed the study if the participant was followed through their last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of study intervention that was received.

Participants will not be considered to have completed the study if consent was withdrawn or the participant was lost to follow-up (see Sections 7.2 and 7.3). The end of study is defined as the last expected visit/contact of the last participant undergoing the study.

4.4.1 Study Stopping Criteria

Discontinuation of specific sites or of the study as a whole are handled in accordance with Appendix A 8.

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

- Two or more (in different participants) reports of new onset symptomatic heart failure confirmed by echocardiography.
- Two or more (in different participants) reports of new onset non-infective colitis confirmed histopathologically.
- Five or more (in different participants) reports of ≥ Grade 4 severity infection (excluding COVID-19 infection), not associated with an asthma exacerbation.
- Two 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 asthma exacerbations) that preclude continuing

dosing of the participant, unless obviously not related to the study drug (eg, motor vehicle accident).

- Participant enrolment is unsatisfactory.
- Non-compliance that might significantly jeopardise the validity or integrity of the trial, or safety of the participant(s).
- Sponsor decision to terminate development.

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 head of the medical institution, where applicable). When feasible, the sponsor will provide advance notice to all participating investigators (or head of the medical institution, 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

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. During the screening period, for any clinical laboratory test where the result is not available from central laboratories prior to randomisation, a result from a local laboratory may be an acceptable alternative but the medical monitor must be consulted first.

5.1 Inclusion Criteria

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

If any criterion cannot be fully assessed at a particular visit (eg, due to awaiting information from the participant's usual physician at SV1 or laboratory results not yet available at SV2), the criterion must be fully assessed prior to randomisation:

Age

1 Participant must be 18 to < 65 years of age inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2 Documented physician-diagnosed asthma of early onset, defined as development of asthma before the age of 25 years. Asthma should be diagnosed > 12 months prior to SV1. Acceptable documentation includes any of the following:

(a) Contemporaneous clinical notes, dated > 12 months prior to SV1 **and** when participants were aged < 25 years, showing a diagnosis of asthma.

(b) Contemporaneous clinical notes or pharmacy records, dated > 12 months prior to SV1 **and** when participants were aged < 25 years, showing on-going treatment for asthma (note: the indication of asthma must be documented).

(c) Investigator documentation based on communication with the physician who treats the participant's asthma.

3 Treated with medium-to-high dose ICS defined as total daily dose of > 250 µg fluticasone dry powder or equivalent (see Appendix F for equivalent ICS doses), for at least 12 months prior to SV1 and on a stable dose for ≥ 3 months prior to SV1.

4 Stable LABA therapy for ≥ 3 months prior to SV1 (this may be as a fixed-dose combination product, or a separate inhaler).

– Treatment with additional asthma controller therapies eg, LAMA, LTRA, theophylline (≥ 1 month at a stable dose) prior to SV1 is allowed. Individuals on theophylline must have normal blood levels documented in the 3 months prior to SV1. Treatment with oral corticosteroids is allowed if dose has been stable for ≥ 3 months.

5 An ACQ-6 score ≥ 1.5 at SV1, SV2, and SV4 (randomisation).

6 Morning pre-BD FEV_1 < 85% predicted normal at SV1.

7 ≥ 70% adherence (days) to eDiary completion both between SV1 and SV2 **and** in the 14 days preceding SV4.

– An adherent day requires completion of evening and subsequent morning diary between SV1 (evening assessment) and SV2 (morning assessment).

8 ≥ 70% adherence to background medication as assessed by eDiary entries both between SV1 and SV2 **and** in the 14 days preceding SV4.

9 Participants must demonstrate ability to perform acceptable inhaler and spirometry techniques.

10 Able and willing to comply with the requirements of the protocol including ability to read, write, be fluent in the translated language of all participants facing questionnaires used at site, and use electronic devices eg, eDiary and spirometry.

Weight

11 Bodyweight ≥ 40 kg and BMI < 40 kg/m^2.

Reproduction

12 For female participants of childbearing potential (see Appendix I for definition of childbearing potential):

- A negative serum pregnancy test at SV1.
- A negative urine pregnancy test at SV2 and prior to administration of study intervention at SV4 (randomisation).

13 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 SV12 (Week 24) of the study. See Appendix I 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.

14 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.

15 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 SV4 (Day 1) through to SV12 (Week 24) 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 SV4 (Day 1) through to SV12 (Week 24) of the study. See Appendix I 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

16 Provision of signed and dated, written informed consent (and any locally required authorisation eg, data privacy) for study participation which includes mandatory

genotyping (study objective). Note: If a participant declines to participate in the mandatory genotyping component of the study, the participant will not be included in the study.

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

Type of Participant and Disease Characteristics

18 Participants with documented evidence of asthma as demonstrated by either:

- Post-BD reversibility of $FEV_1 \geq 12\%$ and ≥ 200 mL (15 to 60 min after administration of 4 puffs of albuterol/salbutamol), within 12 months prior to SV1, or at SV1 or SV2. Note: if the participant cannot perform post-BD spirometry at SV1 or needs to perform a repeat assessment of post-BD spirometry, it is also acceptable to assess this criterion at SV2, **or**
- Positive methacholine challenge test within the 12 months prior to SV1. A positive result is defined as a $PC_{20} \leq 8$ mg/mL.

19 Documented history of ≥ 1 asthma exacerbation in 24 months prior to SV1 (see Section 8.1.5 for definitions of acceptable documentation and asthma exacerbation).

20 Morning pre-BD $FEV_1 \geq 40\%$ predicted normal and > 1 L at SV1.

Criteria to be Assessed for Exploratory Cough Sub-study

Informed Consent

21 Provision of written dated separate ICF for the exploratory cough sub-study.

5.2 Exclusion Criteria

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

Criteria to be Assessed at SV1 and SV2

If any criterion cannot be fully assessed at SV1 and SV2 (eg, laboratory results not yet available), the criterion must be fully assessed prior to randomisation.

Medical Conditions and Diagnostic Assessments

1 Participants with a positive diagnostic PCR test for SARS-CoV-2, the virus responsible for COVID-19, at SV2, or anytime on or after Day -7 and prior to SV4.

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

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

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

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

3 Positive hepatitis C antibody, hepatitis B virus surface antigen, or hepatitis B virus core antibody, at screening; or known to have tested positive for human immunodeficiency virus.

4 Evidence of active or untreated latent TB infection (LTBI):

(a) Positive interferon gamma release assay (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 LTBI, unable to be treated for, or declines treatment of LTBI.

(c) Participants newly diagnosed with LTBI on initial screening could be considered for rescreening if they complete a full course of treatment for LTBI 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 a repeat test and if still indeterminate may be enrolled only after being treated for LTBI.

5 This criterion has been removed.

6 An LVEF < 45% measured by echocardiogram during screening.

7 A family history of heart failure defined as either of the following:

(a) ≥ 2 first degree relatives with clinically significant heart failure, or

(b) ≥ 1 first degree relative with heart failure known to be heritable (eg, hypertrophic cardiomyopathy), unless inheritance is excluded by genetic testing.

8 Major surgery within 8 weeks prior to screening at SV1, or planned inpatient surgery or hospitalisation during the screening, intervention or follow-up periods.

9 Donation of blood or blood products in excess of 500 mL within 3 months prior to SV1.

Prior/Concurrent Clinical Study Experience

10 Participation in a clinical study for a medical device within 3 months prior to screening at SV1.

Other Exclusions

11 Current smokers or recent ex-smokers ie, have quit e-cigarettes or other inhaled tobacco products ≤ 6 months prior to SV1.

12 Ex-smokers with a total smoking history of > 10 pack years (not applicable for e-cigarettes). Note: 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.

Criteria to be Assessed at SV1, SV2, and SV4 (Randomisation)

Medical Conditions and Diagnostic Assessments

13 As judged by the investigator, any evidence of any active medical or psychiatric condition or other reason (prior to randomisation) that 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 that are well controlled.

(b) History of heart failure.

(c) Clinically significant or unstable ischemic heart disease, arrhythmia, 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 using two or fewer medications and stable for at least 6 months.

(f) Known history of primary pulmonary arterial hypertension.

(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 gastroenterologist or by histopathology.

(i) Obstructive sleep apnoea.

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

14 Any clinically important pulmonary disease other than asthma eg, active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, history or planned lung lobectomy, alpha-1 anti-trypsin deficiency, primary ciliary dyskinesia, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis and hyper-eosinophilic syndrome.

15 Any other clinically relevant abnormal findings on physical examination or laboratory testing including haematology, coagulation, serum chemistry, or urinalysis between SV1 and SV4 (randomisation), that in the opinion of the investigator or medical monitor might compromise the safety of the participant in the study or interfere with evaluation of the study intervention. Abnormal findings include, but are not limited to:

(a) ALT or AST > 2 × ULN.

(b) TBL > 1.5 × ULN (unless due to Gilbert's disease).

(c) Evidence of chronic liver disease.

(d) Abnormal vital signs, after 10 minutes of supine rest (confirmed by one controlled measurement), defined as any of the following:

(i) SBP < 80 mmHg or ≥ 150 mmHg.

(ii) DBP < 50 mmHg or ≥ 95 mmHg.

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

(e) Signs of pulmonary oedema or volume overload.

(f) Any clinically significant rhythm, conduction, or morphology abnormalities in the ECG including but not limited to QTcF (Vandenberk et al 2016) > 450 ms.

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

17 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.

18 Current diagnosis of cancer.

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

20 History of allogeneic bone marrow transplant.

21 A helminth parasitic infection diagnosed within 6 months prior to SV4 (randomisation) that has not been treated, or has not responded to SOC therapy.

22 An asthma exacerbation within 8 weeks of SV4 (randomisation; see Section 8.1.5 for definitions of acceptable documentation and exacerbation).

Prior/Concomitant Therapy

23 Receiving any prohibited concomitant medications or therapies as specified in the protocol, as follows:

(a) Identified any time from SV1 through to SV4 (randomisation):

(i) Systemic (oral or injectable) corticosteroids within 4 weeks of SV1 (except as stable maintenance therapy for asthma [see Inclusion Criterion 4]).

(ii) 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 attenuated).

(iii) Ig or blood products within 4 weeks of SV1.

(b) Identified at SV4 (randomisation):

(i) Any immunotherapy within 3 months of SV4 (randomisation), except for stable maintenance dose allergen-specific immunotherapy started at least 4 weeks prior to SV1 and expected to continue through to the end of the follow-up period.

(ii) Interferon gamma within 3 months of SV4 (randomisation).

(iii) Investigational products within 4 months or 5 half-lives of SV4 (randomisation).

(iv) Marketed biologics including dupilumab, benralizumab, and mepolizumab within 4 months or 5 half-lives of SV4 (randomisation), whichever is longer.

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

Prior/Concurrent Clinical Study Experience

24 Concurrent enrolment in another clinical study involving a study intervention.

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

Other Exclusions

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

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

28 Participant has been committed to an institution by virtue of an order issued either by the courts or by a public authority.

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 final administration of study intervention.

5.3.1 Meals, Dietary Restrictions, and Caffeine

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

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

3 During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for 4 hours prior to in-clinic spirometry.

5.3.2 Activity

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

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

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, if there is reason to believe the reason for screen failure was temporary. Only one rescreening per participant is allowed in the study. The timing of the rescreening should be determined by the PI, taking into account the initial reason for screen failure. Prior to rescreening, participants must be reconsented and will retain their original SID number.

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 study protocol.

6.1 Study Interventions Administered

Table 5 Study Interventions

Intervention Name	MEDI3506	Placebo
Type	Biologic	Drug
Dose Formulation	CCI	CCI
Unit Dose Strength	CCI mg/mL C	Not applicable
Dosage Level	CCI mg CCI and CCI mg CCI	CCI
Route of Administration	SC injection	SC injection
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca
Packaging and Labelling	Single vial kits with a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of the vial within the carton). Labels will be prepared in accordance with GMP and local regulatory requirements.	Single vial kits with a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of the vial within the carton). Labels will be prepared in accordance with GMP and local regulatory requirements.

GMP = good manufacturing practice; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; CCI SC = subcutaneous; w/v = weight/volume.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 Dispensation and dosing of study intervention should occur on the same day as allocation of study intervention by the RTSM system.

2 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.

3 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.

4 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 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 passing compatibility tests (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.

A vial should be used only one 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 treatment group is provided (Table 6).

Table 6 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 mg MEDI3506 Treatment Group					
MEDI3506	CCI	CCI	CCI	CCI	CCI
CCI mg MEDI3506 Treatment Group [a]					
MEDI3506	CCI	CCI	CCI	CCI	CCI
Placebo	CCI	CCI	CCI	CCI	
Placebo Treatment Group					
Placebo	CCI	CCI	CCI	CCI	CCI

[a] Do not mix MEDI3506 and placebo in the same syringe.

The dose preparation steps are, as follows:

1 Prepare the assigned MEDI3506 and/or placebo vials for the particular treatment group as per Table 6.
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.
3 Remove the 18-20-gauge needle. Replace with a capped 27-gauge 0.5 inch needle until administration.

6.2.2.1 Treatment Administration

The first day of dosing is considered Day 1 (SV4).

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

MEDI3506 and placebo are not identical in appearance or viscosity. The syringes should be kept out of sight of all blinded persons, including the participant, to maintain the blind. Study intervention will be administered SC by unblinded site personnel via a 27 gauge 0.5 inch needle to the abdomen, back of the arms, or thigh. The 2 injections should be approximately 1 inch (2.5 cm) apart in the same anatomical region. The unblinded site personnel 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 injections of study intervention 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.

At each administration the time of the first injection and anatomical region used for both injections must be documented in the source documents.

6.2.2.2 Monitoring Dose Administration

After the administration of study intervention, vital signs will be assessed according to the SOA, and SC injection sites will be assessed for injection site reactions (Section 8.2.2) by the blinded study team. Participants should be monitored for a minimum of one to 2 hours after administration of study intervention (see 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 recognise and treat anaphylaxis (Appendix H).

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 will be disposed of following site procedures and upon authorization by AstraZeneca, or will be returned to an AstraZeneca-authorised depot if a site is unable to dispose of unused study intervention.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Methods for Assigning Treatment Groups

All participants will be centrally assigned to randomised study intervention using an RTSM. The randomisation will be stratified according to sub-study participation. Before each site is initiated, the log in information and directions for the RTSM will be provided. The RTSM will provide to the investigator(s) or pharmacists the kit identification numbers to be allocated to the participant at the dispensing visit. Routines for this will be described in the RTSM user manual that will be provided to each centre.

Study intervention will be dispensed at the study visits summarised in SOA or per SOC after data cut off.

6.3.2 Methods to Ensure Blinding

This is a double-blinded study in which MEDI3506 and placebo are not identical in appearance or viscosity. Neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants will be aware of the treatment received (ICH E9). 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 treatment 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 treatment 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.

MEDI3506 could reduce eosinophil counts in blood over time. As a precaution, eosinophil, basophil, and monocyte data from the haematology laboratory tests (Table 7) will not be communicated to blinded sponsor or site personnel during the treatment and follow-up periods.

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.

6.3.3 Methods for Unblinding

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

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

The RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a 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 treatment given to participant to the AstraZeneca staff.

If unblinding is required by the DSMB (Appendix A 4), details of the methods for unblinding (sponsor will remain blinded) will be provided in a separate DSMB charter.

The primary analysis (Section 9.1) will be performed after all participants have completed the SV10 (Week 16) assessments or have withdrawn from the study. The sponsor staff will be fully unblinded following the Primary Analysis Clinical Data Lock.

Investigators, participants and site staff will not be made aware of unblinded treatment assignments for individual participants who are in the follow-up period until these participants have completed the study.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the unblinded study site staff.

Participants will receive study intervention from unblinded study site personnel, under medical supervision. The date, and time if applicable, of each 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, along with:

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants are prohibited from receiving certain concomitant medications (described in Section 6.5.4) unless clinically indicated as determined by a physician.

Other than the permitted medications described in the current section, use of concomitant medications or therapies from screening through to the early discontinuation visit/end of study

is discouraged (except where medically necessary). Medications or therapies that are not prohibited and neither compromise participant safety nor affect study data, as judged by the investigator, will be permitted and recorded in the appropriate sections of the eCRF.

6.5.1 Rescue Medicine

Systemic corticosteroid therapy may be used in the case of asthma exacerbation during the study. Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 2 hours following the administration of study intervention. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.5.2 Required Medications

Participants should continue to use the following medications at stable dose and regimen throughout the study, with the exception of medication withhold periods described in Section 6.5.3:

- Medium-to-high dose ICS.
- LABA.
- Any additional asthma controller therapies in use at time of screening eg, LAMA, LTRA, theophylline.

6.5.3 Medication Withhold Periods

Prior to Scheduled Spirometry, AO, and FeNO Measurement

Participants should withhold the following medications for the specified times prior to scheduled spirometry, AO, and FeNO measurement at site:

- SABAs and short-acting muscarinic antagonists for at least 6 hours. In the case of spirometry and AO post administration of study intervention, SABA should be withheld following post-BD spirometry.
- Twice daily LABA and/or LAMA-containing therapies for at least 12 hours.
- Once daily LABA and/or LAMA-containing therapies for at least 24 hours.
- LTRA for at least 24 hours.
- Twice daily theophylline for at least 12 hours.
- Once daily theophylline for at least 24 hours.

Note: for visits where in-clinic spirometry is performed post-administration of study intervention, the medications should be withheld until all spirometry assessments are complete.

Additionally, participants should withhold all BD medications for 4 hours prior to at-home spirometry assessments, where possible.

6.5.4 Prohibited Medications

The inclusion and exclusion criteria sections of the protocol define concomitant medications that, if taken in the period prior to randomisation, would lead to participant screen failure.

In addition, unless clinically indicated as determined by a physician, participants are not permitted to receive any of the following (for the time periods stated):

- Any immunosuppressive or immunomodulator therapies (other than corticosteroids): not allowed 12 weeks prior to randomisation, during screening and until at least Week 16, unless there is a medical need as judged by the investigator.
- Any immunotherapy including allergen immunotherapy: not allowed 12 weeks prior to randomisation, during screening and until at least Week 16, unless there is a medical need as judged by the investigator.
- Immunoglobulin therapy including (IFN-γ) or blood products: not allowed 30 days prior to SV1, during screening and until at least Week 16, unless there is a medical need as judged by the investigator.
- Live or attenuated vaccines: not allowed 30 days prior to the date of randomisation, and during the study including the follow-up period. (Note: Vaccines with adenoviral vectors that are unable to replicate, eg, ChAdOx1, are not considered live attenuated).
- Vaccination against COVID-19 (either first or subsequent dose) within 30 days before randomisation or within 7 days before or after any dose of study intervention.
- Study interventions other than MEDI3506 or placebo are not allowed in the screening period to follow-up period inclusive.
- Marketed biologics are not allowed in the screening period to follow-up period inclusive.
- Long-acting beta-agonists as a reliever (eg, Symbicort Maintenance and Reliever Treatment): not allowed 15 days prior to SV1, during screening and until at least Week 16, unless there is a medical need as judged by the investigator.
- Suplatast tosilate (T2 cytokine inhibitor): not allowed within 15 days prior to SV1, during screening and until at least Week 16, unless there is a medical need as judged by the investigator.

The activity of cytochrome P450 (CYP450) enzymes can be altered by increased levels of certain cytokines (eg, IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation (Huang et al 2010). Thus, MEDI3506, through its downstream mechanism of action, has the potential to normalise the formation of CYP450 enzymes indirectly, through the alteration of local and systemic cytokine levels. However, a role for IL-33 in the regulation of CYP450 enzymes has not been reported. As a precaution, upon initiation or discontinuation of MEDI3506, in patients who are receiving concomitant drugs that have a narrow therapeutic

index and are CYP450 substrates (eg, warfarin), the investigator should consider whether (increased) monitoring is indicated.

6.5.5 COVID-19 Vaccination

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

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

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

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

6.6 Dose Modification

Not applicable.

6.7 Intervention after the End of the Study

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

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 SAE of ≥ Grade 4 severity (see Appendix B 2).

5 Any SAE that is in the Cardiac Disorders system organ class.

6 Confirmed diagnosis of new onset of heart failure and/or progression of heart failure during the study, regardless of severity. For a participant with a suspected new onset of heart failure and/or progression of heart failure, the participant will discontinue and should not be administered study intervention unless and until agreed by the investigator and medical monitor that study intervention may continue to be administered until the diagnosis is confirmed or refuted.

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 randomisation, the participant meets ≥ 1 of the exclusion criteria (Section 5.2) or fails to meet all of the inclusion criteria (Section 5.1) for study participation, unless the PI and medical monitor agree the participant may continue receiving study intervention.

10 The participant misses [redacted] consecutive doses.

11 Following randomisation, receipt of prohibited medication (Section 6.5.4).

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

See the SOA (Table 2) for data to be collected at the time of E/D and follow-up, and for any further evaluations that need to be completed.

7.1.1 Missed doses

A participant not attending for a scheduled dose can continue study intervention at the next scheduled visit. Refer to Section 2.3.1.2 for information on dealing with missed doses as a result of the COVID-19 pandemic.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an E/D visit should be conducted, as shown in the SOA (Table 2). 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 ICF 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SOA (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, methacholine challenge results) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SOA. This excludes all central laboratory assessments, eosinophil counts and NT-proBNP, which need to be performed centrally.

8.1 Efficacy Assessments

8.1.1 In-clinic Spirometry

8.1.1.1 General requirements

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

The vendor providing central spirometry is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate vendor manual.

Participants should follow the relevant medication and other restrictions beforehand (Sections 6.5.3 and 5.3). If any of the specified restrictions are not met, and the assessment cannot be sufficiently delayed on the day, the assessment should be rescheduled within the allowed visit window.

Time of day for scheduled in-clinic spirometry

Spirometry will be performed at specified visits as detailed in the SOA (Table 1 and Table 2). For all participants, spirometry testing must be initiated between 6:00 AM and 11:00 AM during the screening or re-screening period, and randomisation visit (SV4).

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

Spirometry technique

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

Spirometry reference (predicted) values

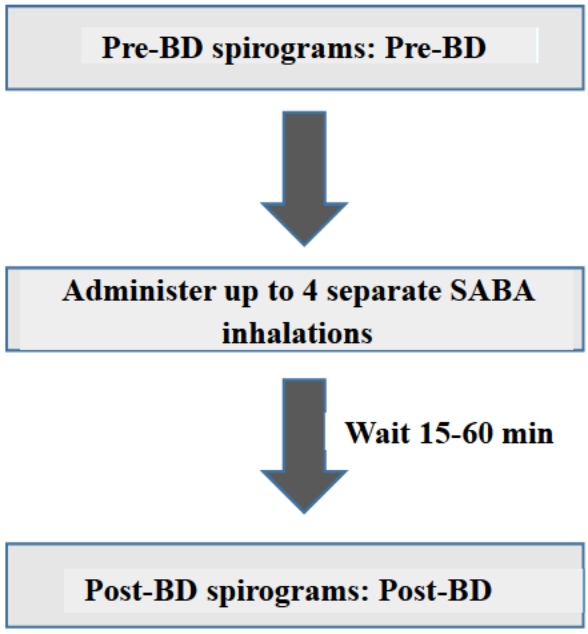
The Global Lung Function Initiative equations will be used to determine the PNV and are pre-programmed into the spirometer.

FEV_1, expressed as percent of the PNV, will be calculated as follows:

FEV_1% of PNV = (FEV_1 measured/FEV_1PNV) × 100

Bronchodilatation can be induced using albuterol (90 µg metered dose), salbutamol (100 µg metered dose) or levalbuterol (45 µg metered dose) up to a maximum of 4 inhalations. It is highly recommended to use a spacer device for this procedure. The algorithm for reversibility testing is outlined in Figure 2.

Figure 2 Reversibility algorithm



BD = bronchodilator; min = minutes; SABA = short-acting beta agonist.

After a gentle and complete exhalation, up to a maximum of 4 inhalations of salbutamol (100 µg metered dose) or albuterol (90 µg metered dose) should be administered using a spacer device. In rare cases where a participant has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol (45 µg metered dose, up to a maximum of 4 inhalations) can be used (Sorkness et al 2008). A nebuliser should not be used. A lower total dose (eg, 2 inhalations instead of 4 and if required up to a maximum of 4 puffs) can be used if there is a concern about any effect on the participant's safety; the reason should be noted in the participant's medical record.

The highest technically acceptable pre- and post-BD FEV_1 will be used to determine reversibility.

Reversibility is calculated as follows:

FEV_1% Reversibility = (post-BD FEV_1 - pre-BD FEV_1)/pre-BD FEV_1 × 100

Full details will be included in the vendor manual.

Record keeping

A signed and dated copy of the pre- and post-BD printout must be kept at study sites 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 At-home Spirometry

During the study period, participants will be required to monitor lung function at home twice daily using an at-home spirometry device. Participants should follow the relevant medication and other restrictions beforehand (Section 5.3.2 and Section 6.5.3). Further details will be provided in a separate instruction manual.

8.1.3 Airwave Oscillometry

Airwave oscillometry will be performed at specified visits as detailed in the SOA (Table 1 and Table 2). Airwave oscillometry is a non-invasive lung function test included in this study to evaluate treatment effect on small airway physiology. By measuring participant's airflow and response to sound waves, frequency-dependent resistance and reactance will be calculated by the AO system software.

A calibrated system will be used for AO measurements (equipment to be provided by vendor). Detailed procedures for performing, recording and analysing AO data will be described in a separate manual. Details regarding assessment of the quality of AO and the BTR process will also be detailed in the manual and in the Monitoring plan. Prior to scheduling and performing AO assessments, the following should be observed:

- Participants should perform AO prior to pre-BD spirometry assessments if both tests are to be performed on the same visit.
- Participants should observe the relevant lifestyle restrictions (see Section 5.3) prior to AO assessments.
- Participants should observe the medication withhold periods (see Section 6.5.3) prior to AO assessments.

If any of the above restrictions are not met, and the assessment cannot be sufficiently delayed on the day, the assessment should be rescheduled within the allowed visit window (Table 2).

A signed and dated copy of the results printout from the equipment must be kept at the study site for source data verification. The printout must be marked with the study code, SID, date and time of measurement, and visit number. A number of parameters including (but not limited to) R5, R20 and AX for each assessment will be recorded and analysed. The AO assessment at SV6, SV7, SV8, SV9, and SV10 will be performed only if the baseline visit AO is performed successfully, as judged by the investigator.

8.1.4 Fractional Exhaled Nitric Oxide

Airway inflammation will be evaluated using a standardised single-breath FeNO test in accordance with the SOA (Table 1 and Table 2). A single exhalation technique recommended by the manufacturer will be followed (Allakhverdi et al 2007; Alving et al 2017).

The FeNO test will be performed prior to AO and spirometry. Participants should follow the relevant medication and other restrictions beforehand (Sections 6.5.3 and 5.3). If any of the above restrictions are not met, and the assessment cannot be sufficiently delayed on the day the assessment should be rescheduled within the allowed visit window.

The NIOX VERO® Airway Inflammation Monitor will be used to measure FeNO. Instructions for use of this monitor will be provided in a separate user's manual.

NIOX VERO® sensors will be replaced as recommended by the manufacturer. The vendor supplying the equipment will be responsible for ensuring that the equipment and procedures for the measurement of FeNO are validated prior to the start of the study.

If possible, all post-randomisation FeNO assessments should be performed within ± 1.5 hours of the time that the randomisation FeNO was performed.

8.1.5 Asthma Exacerbations

Definition of Asthma Exacerbation

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

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

c. An in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours).

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

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

Assessment and Documentation of an Asthma Exacerbation

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

- Discharge summaries from a hospital, emergency room, or an urgent care facility indicating that a participant was hospitalised/treated with systemic corticosteroids for an asthma exacerbation.
- Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic corticosteroids.
- Evidence of prescriptions for systemic corticosteroids used during an exacerbation.
- A documented conversation between the Investigator (or delegate) and a participant who is already on an OCS action plan, including the information necessary to assess Inclusion Criterion 19.
- A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with corticosteroids at their clinic or under their supervision. The dates (month/year) of the exacerbations and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

The guidance below defines assessment of asthma exacerbations.

- The start of an exacerbation is defined as the earliest of the following:
  - Start date of systemic corticosteroids or temporary increase in a stable OCS background dose.
  - Date of emergency room or urgent care visits requiring systemic corticosteroids.
  - Date of hospital admission due to asthma.
- The end date of an exacerbation is defined as the latest of the following:
  - Last date of systemic corticosteroids or temporary increase in a stable OCS background dose.
  - Date of discharge from emergency room or urgent care visit.
  - Date of hospital discharge.

- If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation in the statistical analysis.
- All asthma exacerbations that occur during the treatment period and follow-up, must be recorded in the exacerbation eCRF. See Section 8.3.6 for additional information on recording asthma exacerbations as an AE/SAE during the study.

eDiary data and Exacerbations

Any sustained increase in asthma symptoms as reported via the eDiary (that do not meet the definition of criteria of an asthma exacerbation) will be graded as a worsening of asthma. Specifically:

- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline or use of 12 puffs/day on any one day, and/or
- An additional nebulised β2 agonist use on at least 2 consecutive days compared with the average use during baseline, and/or
- An increase of 2 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with the average during baseline, and/or
- ≥ 6 out of previous 7 nights with awakenings due to asthma requiring rescue medication

Alerts to study site will be triggered for participants who experience a drop in PEF ≥ 30% on 2 consecutive days.

If an asthma exacerbation event is not associated with at least one of the above eDiary data deterioration criteria, the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

Participants will be required to keep a record of their asthma symptoms in the eDiary as per the SOA (Table 1 and Table 2). The data captured in the eDiary will also be used to determine individuals CompEx events.

8.1.6 CompEx

CompEx is a combination of exacerbations of asthma and diary events (ie, combination of eDiary variables). CompEx is a composite surrogate endpoint for exacerbations of asthma, recently developed by AstraZeneca (it is not yet a regulatory-approved clinical endpoint). Diary events are defined by the threshold and slope criteria using the following morning/evening (AM/PM) diary variables:

- PEF
- Symptom score (0 – 3)

- Use of rescue medication

CompEx can predict treatment efficacy on exacerbations in early development before running traditional long-term exacerbation trials. CompEx can be used broadly in the assessment of new therapeutic interventions for asthma (Fuhlbrigge et al 2017; note: the referenced publication used the term 'severe exacerbation' but used the same definition as used for 'exacerbation' in this protocol; therefore, the term 'exacerbation' has been used in this section for internal consistency of the protocol.)

8.1.7 VitaloJAK Cough Monitor (Exploratory Cough Sub-study Only)

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.

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 is recorded correctly.

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

Participants will be monitored for 24 hours following SV2 and SV10, and set up of the cough monitors should be performed as the final assessment at each of these visits.

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

8.1.8 Participant Reported Outcome Questionnaires

Participants will complete the PRO questionnaires on an electronic device (Section 8.1.8.1) supplied to the site according to the SOA (Table 1 and Table 2). PRO questionnaires to be completed at the site visits must be completed prior to treatment administration and ideally before any discussions of health status or other study procedures, such as collection of laboratory samples to avoid biasing the participant' s responses to the questions. All within-window PRO assessments for the morning and evening assessments at home should be completed within this set time window programmed into the device and will notify the participant when it is time to respond to the questions.

8.1.8.1 Daily eDiary

During the study period, participants will be required to take their asthma controller therapy regularly and complete an eDiary twice daily.

At SV1, participants will receive a handheld eDiary device to complete twice-daily, daily and non-daily PRO assessments during the study. Participants will be provided training on the use of the handheld device. Daily assessments will include night-time and daytime asthma symptoms (morning and evening diary, respectively), use of inhaled rescue medication in response to worsening symptoms, nights with awakenings due to asthma symptoms (morning diary only) and background medication use. The PEF data (obtained from the home peak flow meter) will be captured at the conclusion of the morning and evening eDiary entry.

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

The number of doses of rescue medication (1 dose unit = 1 puff on inhaler) taken will be recorded by the participant in the eDiary twice daily. The number of inhalations taken between the morning and evening lung function assessments will be recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments will be recorded in the morning.

Nocturnal awakenings due to asthma symptoms will be recorded by the participant in the daily eDiary each morning by answering the question whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response.

Background (inhaled ICS/LABA) medication administration use will be recorded once daily in the daily eDiary as “yes” or “no” response.

The eDiary questions support the analysis of a novel endpoint called CompEx (Section 8.1.6).

8.1.8.2 Cough Visual Analogue Scale (Exploratory Cough Sub-study Only)

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

8.1.8.3 Asthma Control Questionnaire-6

The ACQ (Juniper et al 1999) was developed to measure asthma control and has been fully validated for use in adults and children 6 to 17 years of age. International guidelines for the treatment of asthma have identified that the primary clinical goal of asthma management is to

optimise asthma control (minimisation of symptoms, activity limitation, bronchoconstriction, and rescue BD use) and thus reduce the risk of life-threatening exacerbations and long-term morbidity. The ACQ was developed to meet these criteria by measuring both the adequacy of asthma control and change in asthma control, which occur either spontaneously or as a result of treatment.

In the ACQ-6, participants are asked to recall how their asthma has been during the previous week by responding to one BD use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. Mean scores of ≤ 0.75 indicate well-controlled asthma, scores between 0.75 and ≤ 1.5 indicate partly controlled asthma, and scores > 1.5 indicate not well-controlled asthma (Juniper et al 2006). Individual changes of at least 0.5 are considered clinically meaningful.

The questionnaire will be completed using the eDiary in accordance with the SOA (Table 1 and Table 2).

8.1.8.4 St George's Respiratory Questionnaire

The SGRQ is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into two parts: part one 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 three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment.

Specific details on the scoring algorithms are provided by the developer in a user manual (Jones and Forde 2009). The SGRQ will be completed using the eDiary in accordance with the SOA, and a 4-week recall version will be used.

8.1.8.5 Sino-nasal Outcome Test-22

The SNOT-22 is a condition-specific health-related quality of life assessment, which captures participant-reported physical problems, functional limitations, and emotional consequences of sinonasal conditions (Hopkins et al 2009; Piccirillo et al 2002). The SNOT-22 contains a list of 22 symptoms and social/emotional consequences of a participant's nasal disorder, and measures how severe each symptom is and the social/emotional consequences of symptoms over a 2-week period on a scale from 0 (no problem) to 5 (problem as bad as it can be). The total score is the sum of item scores and has a range from 0 to 110 (higher scores indicate poorer outcomes).

The SNOT-22 will be administered to participants who have comorbid chronic inflammatory conditions of the nasal mucosa and/or paranasal sinuses (CRS) on the eDiary according to the SOA (Table 1 and Table 2).

8.1.8.6 Patient Global Impression of Benefit/Risk

The patient global impression of benefit/risk is a 5-item questionnaire assessing the participant's perception of the overall benefits and risks of treatment. The 5 items assess: overall trial experience, efficacy, side effects, convenience and overall assessment of the benefits and harms of treatment. Items are rated on 5- or 6-point verbal rating scales.

8.1.8.7 Study Participant Feedback Questionnaire

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

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SOA (Table 1 and Table 2).

8.2.1 Medical, Surgical, and Asthma History

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

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

8.2.2 Physical Examinations, Weight, and Height

- Complete and brief physical examinations will be performed by a licensed healthcare provider (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 (Table 1 and Table 2).

8.2.3 Vital Signs

The nominal timing of vital signs, ECGs, and blood draws is described in the SOA (Table 1 and Table 2). 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 [redacted] 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 final [redacted] 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

The nominal timing of vital signs, ECGs, and blood draws is described in the SOA (Table 1 and Table 2). 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 SV4 (randomisation), 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. ECGs 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 PI for clinical significance.

Electrocardiogram variables will be collected as follows:

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

8.2.5 Echocardiograms

A transthoracic echocardiogram to assess left ventricular ejection fraction will be performed and read locally according to the SOA (Table 1 and Table 2).

8.2.6 SARS-CoV-2 Serology Testing

Participants' serum will be tested for the presence of antibodies to the SARS-CoV-2 virus from blood drawn at the visits indicated in the SOA (Section 1.3).

8.2.7 Clinical Safety Laboratory Assessments

The nominal timing of vital signs, ECGs, and blood draws is described in the SOA (Table 1 and Table 2). 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 (note: during the screening period, for any clinical laboratory test where the result is not available from central laboratories prior to randomisation, a result from a local laboratory may be an acceptable alternative but the medical monitor must be consulted first).

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).

All local laboratory results will be recorded/filed in the source notes.

The laboratory variables listed in Table 7 will be measured in this study.

Table 7 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
WBC count with differential	Potassium
RBC count	Sodium
Haematocrit	AST
Platelet count	ALT
Haemoglobin	ALP
Coagulation parameters (PT, INR, and aPTT)	TBL (if result is > 1.5 ULN, indirect and direct bilirubin will be measured)
	GGT
Urinalysis (dipstick)	Creatinine
Colour and appearance	Blood urea nitrogen
Specific gravity	Albumin
pH	Total protein
Protein	Uric acid
Microscopy including WBCs, RBCs, and casts.	
Glucose	
Ketones	
Blood	
Bilirubin	
Leukocytes	

Note for haematology: blinding procedures for eosinophil, basophil, and monocyte data are described in Section 6.3.2.
Note for serum chemistry: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.
ALP = alkaline phosphatase; ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; PT = prothrombin time; RBC = red blood cell; TBL = total bilirubin; ULN = upper limit of normal; WBC = white blood cell.

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 Hy's Law', for further instructions.

Pregnancy Test

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

Other Safety Tests

- FSH (if needed to confirm post-menopausal status in female participants aged < 50 years and not on HRT).
- HbA1c.
- Hepatitis B (HbsAg, anti-HBs, and anti-HBc) and C antibodies.
- HIV-1 and HIV-2 antibodies.
- IGRA (TB test). See Exclusion Criterion 4.

- Serum tryptase will only be taken in the event of suspected anaphylaxis (Appendix G and Appendix H).
- NT-proBNP.
- SARS-CoV-2 PCR test.

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 will be collected from signing of ICF throughout the treatment period and including the follow-up period. SAEs will be recorded from the time of signing of ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall report the SAE to the sponsor within 24 hours.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at SV12 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 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.

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'.

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

8.3.4 Disease Under study

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

8.3.5 Adverse Events Based on Signs and Symptoms

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

8.3.6 Adverse Events Based on Examinations and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-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 treatment, eg, dose adjustment or drug interruption).

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

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

8.3.7 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 characterise 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 Hy's Law as described in Section 8.3.8.
- 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, SARS-CoV-2 and all other opportunistic infections listed in the Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (NIH 2019).
- Gastrointestinal adverse events.
- Malignancy.

8.3.8 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 total bilirubin ≥ 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.

8.3.9 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 one 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.

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

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 abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital 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 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 relevant information is provided to the AstraZeneca Patient Safety data entry site within one or 5 calendar days for SAEs (see Section 8.3.9) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.3.10.2 Paternal Exposure

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

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until the end of the follow-up period (SV11 [Week 16]) or date of last contact 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 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 relevant information is completed within one (Initial Fatal/Life-Threatening or follow-up

Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error 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 protocol.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, the investigator or other site personnel will 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 Sample Biomarkers

8.5.1 Human Biological Samples

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

- Samples will be stored for a maximum of 15 years after the end of the study 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 six 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. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years after the end of the study. Additional use includes but is not limited to further characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.2 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of MEDI3506 as specified in the SOA (Table 1 and Table 2).
- 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.
- Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.
- Samples from participants who receive placebo may be analysed at minimum selected time points to confirm no dosing with MEDI3506 took place.

8.5.2.1 Determination of Drug Concentration

The nominal timing of vital signs, ECGs, and blood draws is described in the SOA (Table 1 and Table 2). The time of the first SC injection will be recorded for each participant as the timings will be required for analysing the PK data.

Serum will be collected to evaluate the PK of MEDI3506 according to the SOA. MEDI3506 concentration in serum will be measured utilizing a validated assay method.

Instructions for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites.

8.5.3 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 titre assay components. Full details of the methods used will be described in a separate report.

ADA samples may also be further tested for characterisation of the ADA response, including possible assessment of neutralising antibody.

Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

8.5.4 Pharmacodynamics

There are no established PD measures for MEDI3506. For exploratory biomarkers that may indicate a PD effect, see Section 8.5.5.

8.5.5 Collection of Mandatory Samples for Biomarker Analysis

- Samples for biomarker research are required and will be collected from all participants in this study as specified in the SOA (Table 1 and Table 2).
- Samples include the following:
  - Nasal mucosal sampling. Nasal mucosa (for mRNA) is collected using a sterile, disposable nasal mucosal collection device to curette a sample of nasal mucosa for analysis.
  - Nasal mucosal lining fluid. Nasal mucosal lining fluid is collected using the Nasosorption™ FX·i device, which is gently applied to the nasal mucosa to absorb mucosal lining fluid from mucosal surfaces.
  - Whole blood for RNA PAXgene. RNA PAXgene will be used for the collection, transport, and storage of whole blood, and the stabilization of intracellular RNA. RNA transcript profiling analyses will be performed on RNA PAXgene samples.

Note: If nasal mucosal sampling for mRNA at SV4 (randomisation) is deemed by the investigator to have been challenging for individual participant tolerability (eg, due to nasal polyps), subsequent nasal sampling may be omitted at the investigator's discretion.

Biological samples will be collected at specified visits as detailed in the SOA (Table 1 and Table 2):

- Total IgE (serum).
- Allergen-specific IgE (serum).
- EDN (plasma).
- sST2 (serum).

- Exploratory serum biomarkers, including but not limited to:
  - CCI
  - IL-5 (serum).
  - IL-13 (serum).
  - TSLP (serum).
- IL-33 isoforms (nasal lining fluid).
- mRNA transcriptome (blood and nasal mucosal sample).
- Pharmacogenetic sampling (blood):
  - CCI
  - CCI
    - CCI

For storage, re-use and destruction of human biological samples, see Appendix C.

8.5.6 Other study related biomarker research

Already collected samples may be analysed on different biomarkers thought to play a role in asthma including, but not limited to, serum analytes, or tissue biomarkers and/or specific candidate genes/genome-wide analysis for RNA, to evaluate their association with observed clinical responses to MEDI3506.

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

8.6 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SOA (Table 1 and Table 2) and is subject to agreement in the ICF.

A blood sample for this genetic research will be obtained from the participants at SV4. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not

drawn at SV4, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

For storage and destruction of genetic samples, see Appendix D.

8.7 Health Economics

Not applicable.

8.8 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 form at each study visit, according to the SOA (Table 1 and Table 2).

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is the change from baseline in pre-BD FEV_1 at Week 16. A treatment policy estimand will be applied whereby all available data are included in the analysis, irrespective of whether a participant discontinued study intervention or received rescue therapy.

The null hypothesis is that the change from baseline in FEV_1 at Week 16 for participants dosed with MEDI3506 is equal to the change from baseline in FEV_1 at Week 16 for participants dosed with placebo. The alternative hypothesis is that the change from baseline in FEV_1 at Week 16 for participants dosed with MEDI3506 is greater than the change from baseline in FEV_1 at Week 16 for participants dosed with placebo, ie:

- H0: Change from Baseline in FEV_1 at Week 16 (MEDI3506-placebo) = 0.
- H1: Change from Baseline in FEV_1 at Week 16 (MEDI3506-placebo) > 0.

Hypothesis testing will be performed at the one-sided 10% level. If the p-value is < 0.1, reject H0 and accept H1. A hierarchical testing strategy will be used to preserve the type I error for the comparisons of each of the 2 dose levels of MEDI3506 versus placebo, as follows:

- Step 1: Test MEDI3506 600 mg versus placebo in regard to H0
- Step 2: If previous step rejects: test MEDI3506 300 mg versus placebo in regard to H0

9.2 Sample Size Determination

A sample size of 216 participants (72 participants per treatment group), randomised 1:1:1 to MEDI3506 CCI mg: MEDI3506 CCI mg: placebo, will provide at least 80% power to detect a statistically significant difference in change from baseline to Week 16 in pre-BD FEV_1,

assuming a difference of 150 mL between placebo and MEDI3506, a between-participant SD of 420 mL and a one-sided- 10% alpha level. To allow for 5% participants being ineligible for the primary analysis, a total of approximately 228 participants will be randomised (approximately 76/arm).

Up to 60 participants are intended to be included in the cough sub-study (ie, approximately 20 participants per treatment group). However, given the exploratory nature of the sub-study and that it may not be activated in all countries, randomisation of participants not included in the sub-study will not be restricted, therefore, sub-study recruitment may not be achieved. Since limited data are available on cough monitoring in this population, the sub-study is considered exploratory and no formal power calculations have been performed.

9.3 Populations for Analyses

The following populations are defined:

Table 8 Populations for Analysis

Population/Analysis set	Description
ITT population	Participants who are randomised and receive any study intervention. Participants will be analysed according to their randomised treatment group.
As-treated Population	Participants who are randomised and receive any study intervention. Participants will be analysed according to the treatment 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 analysed according to the treatment they actually receive.

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

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

9.4 Statistical Analyses

All personnel involved with the analysis of the study will remain blinded until Primary clinical data lock and until Clinical Study Protocol deviations are identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will be developed and finalised before Primary clinical data 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 16 (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 16, irrespective of whether the participant discontinued study intervention or received rescue therapy.

Demography and baseline characteristics will be summarised by treatment group for the ITT population.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

The difference in mean change from baseline in FEV_1 at Week 16 (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 16, irrespective of whether the participant discontinued study intervention or received rescue therapy. No imputation will be made for missing data, as a repeated measures model is being applied. The model will include fixed effects for baseline, visit, treatment and the baseline by visit and treatment by visit interactions.

The significance of the treatment effect will be tested at a 10% one-sided level of significance as described in Section 9.1.

9.4.2.2 Secondary and Exploratory Endpoints

Change from baseline in ACQ-6, SGRQ and AO parameters will be analysed using a repeated measures analysis of covariance model, similar to that described for the primary efficacy analysis (Section 9.4.2.1). PRO responder endpoints at Week 16 will be analysed using a chi-squared test.

Objective cough measurements will be analysed using analysis of covariance, and may be log-transformed prior to analysis. Estimates of the least square mean change from baseline for each treatment, and the difference between them, together with 80% confidence interval and one-sided p-values, will be obtained from the model for each visit.

Time to first CompEx event and time to first asthma exacerbation will be analysed using a Cox proportional hazard model, with treatment fitted as a covariate. The data will also be displayed in a Kaplan-Meier plot. The CompEx event rate will be analysed using negative

binomial regression, with the log(follow-up time) included as an offset term. The dependent variable will be the number of CompEx events through Week 16, and the model will include treatment group as a fixed effect. All available data from participants through to Week 16 will be included, irrespective of whether they discontinued study intervention.

Change from baseline to Week 16 in concentration of FeNO will be analysed using a repeated measures analysis of covariance model, similar to that described for the primary efficacy analysis (Section 9.4.2.1). Where appropriate, endpoints may be log-transformed prior to analysis. Estimates of the least square mean change from baseline for each treatment, and the difference between them, together with 80% confidence interval and one-sided p-values, will be obtained from the model for each visit.

The difference in mean change from baseline in post-BD FEV_1, and the change in FEV_1 % reversibility at Weeks 8 and 16 will be estimated using a repeated measures mixed effects analysis of covariance model, similar to that described for the primary efficacy analysis (Section 9.4.2.1).

The composite estimand will be the difference between MEDI3506 and placebo response rate at Week 16 in the ITT population. Participants with missing data at Week 16 will be considered non-responders. For each MEDI3506 group compared with placebo, the odds ratio and 80%, and one-sided p-values will be reported.

9.4.3 Subgroup Analyses

Subgroup analyses may be performed and will be described in the SAP.

9.4.4 Safety

The occurrence of AEs and SAE 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 summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit. Laboratory measurements will also be summarised 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 summarised at each visit. Change from baseline in vital signs will be summarised by visit.

9.4.5 Other Analyses

9.4.5.1 Immunogenicity and PK

Positive antibodies to MEDI3506 will be reported by treatment 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 biomarkers, 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 modelling may be performed if data allow, but will not be reported in the CSR. The potential correlation between PK exposure and biomarkers, and efficacy/safety response may be evaluated.

9.4.5.2 Exploratory Biomarker Outcomes

Change from baseline in blood eosinophils, EDN, total IgE and blood neutrophils will be analysed using a repeated measures analysis of covariance model, similar to that described for the primary efficacy analysis, in Section 9.4.2.1. Where appropriate, endpoints may be log-transformed prior to analysis. Estimates of the least square mean change from baseline for each treatment, and the difference between them, together with 80% confidence interval and one-sided p-values, will be obtained from the model for each visit.

Full details of all other exploratory biomarker outcomes will be provided in the SAP.

9.4.5.3 Exploratory Analyses

Full details of all other exploratory analyses will be provided in the SAP.

9.5 Interim Analyses

No formal interim analyses are planned for this study.

The primary analysis will occur once all participants have either completed the SV10 (Week 16) assessments or have withdrawn from the study. The sponsor staff will be fully unblinded following the Primary Analysis Clinical Data Lock. Investigators, participants and site staff will not be made aware of unblinded treatment assignments for individual participants who are in the follow-up period until these participants have completed the study. The final analysis will occur when all participants have completed the follow-up period at SV12 (Week 24) or have withdrawn from the study.

9.6 Data Monitoring Committee

An independent unblinded DSMB will perform evaluations of safety data, from this study and Studies D9180C00002 (in participants with COPD), D9182C00001 (in participants with AD) and D9183C00001 (in participants with DKD). 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.

For details on the DSMB, refer to Appendix A 4.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies (except those using medical devices), investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 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 3 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 4 Committee's 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 5 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 study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 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 inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the 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, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 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 7 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 source data verification plan.

A 8 Study and Site Start and Closure

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

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

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

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

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any 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.

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

B 1 Definition of Adverse Events

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

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

B 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-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.

AEs 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 oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

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

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

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

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.

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 subject.

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 subject.

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 a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

B 4 Medication Error

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

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

Medication error includes situations where an error:

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

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

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature

- Wrong participant received the medication (excluding RTSM errors)
- Wrong drug administered to participant (excluding RTSM errors)

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

- Errors related to or resulting from RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or SOC 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 analysed, AstraZeneca is not obliged to destroy the results of this research.

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with 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 Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on MEDI3506 continues but no longer than 15 years after the end of the study or other period as per local requirements.

D 2 Genetic Research Plan and Procedures

Selection of genetic research population

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

Inclusion criteria

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

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.
- Healthy volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of consent

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

Collection of samples for genetic research

The blood sample for this genetic research will be obtained from the participants at SV4 (randomisation). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at SV4, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and storage of DNA samples

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

Ethical and regulatory requirements

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

Informed consent

The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the

original filed at the study centre. The PI is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant data protection

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

Data management

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

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

E 1 Introduction

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

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

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

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

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the 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
AST 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
AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For 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.

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

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

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

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

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

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria not met

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

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

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

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

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

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

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the 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 a SAE:

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

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

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

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

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

E 6 Laboratory tests

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV 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	Carbohydrate deficient transferrin (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.
CMV = cytomegalovirus; EBV = Epstein-Barr virus GGT = gamma glutamyl transferase; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV hepatitis C virus; HEV = hepatitis E virus; Ig = immunoglobulin; INR = international normalised ratio; LDH = lactate dehydrogenase.

E 7 References

1 Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

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

Appendix F Maintenance Therapy Equivalence Table

Estimated daily doses for ICS.

Asthma Therapy	Total Daily Dose (µg/day)	
	Medium	High
ICS [a]		
Beclomethasone dipropionate (CFC)	> 500 to 1000	> 1000
Beclomethasone dipropionate (HFA)	> 200 to 400	> 400
Budesonide	> 400 to 800	> 800
Ciclesonide	> 160 to 320	> 320
Fluticasone furoate (eg, Arnuity® Ellipta® Breo®)	N/A	200
Fluticasone propionate	> 250 to 500	> 500
Fluticasone propionate (HFA)	> 250 to 500	> 500
Mometasone furoate	> 220 to 440	> 440
Triamcinolone acetonide	> 1000 to 2000	> 2000
ICS in ICS/LABA combination [a]		
Beclomethasone dipropionate (eg, Fostair®)	> 200 to 400	> 400
Fluticasone propionate (HFA; eg, Seretide®, Advair®)	> 250 to 500	> 500
Fluticasone furoate (eg, Relvar® Ellipta®, Breo® Ellipta®)	N/A	184 to 200
Budesonide, if as delivered dose (eg, Symbicort®)	> 400 to 640	> 640
Mometasone Furoate (eg, Dulera®)	> 220 to 400	> 400

[a] The ICS doses were derived from GINA 2018 and the ICS/LABA combinations were derived from GINA 2017 and 2018 and using prescribing information.

CFC = chlorofluorocarbon propellant; GINA = Global Initiative for Asthma; HFA = hydrofluoroalkane propellant; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; N/A = not applicable.

Appendix G 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 recognise 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, generalised hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   (a) Respiratory compromise (eg, dyspnoea, 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, generalised hives, itch-flush, swollen lips-tongue-uvula).
   (b) Respiratory compromise (eg, dyspnoea, 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: SBP of less than 90 mmHg or greater than 30% decrease from that participant'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 H).

Appendix H Signs, 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 recognise 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.

H 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 oedema.
- 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.
- Rhinorrhoea.
- Change in voice.
- Metallic taste.
- Nausea, vomiting, diarrhoea, abdominal cramps, and bloating.
- Lightheadedness.
- Headache.
- Uterine cramps.
- Generalised warmth.

H 2 Management of Acute Anaphylaxis

H 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.

H 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.

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

1 Consider epinephrine infusion.

2 Consider H1 and H2 antihistamines.

3 Consider nebulised 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 SF, Lockey RF, Simons FE; World Allergy Organization ad hoc Committee on Epinephrine in Anaphylaxis. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. Allergy. 2008;63(8):1061-70.

Appendix I Contraception Guide

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

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

For females 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 females 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 I9.

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

Table I9 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomised 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 J Abbreviations

Abbreviation or special term	Explanation
ACM	Ambulatory cough monitoring
ACQ	Asthma control questionnaire
AD	Atopic dermatitis
ADA	Anti-drug antibody(ies)
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
anti-HBc	Antibody to hepatitis B core antigen
anti-HBs	Antibody to hepatitis B surface antigen
AO	Airwave oscillometry
AST	Aspartate transaminase
ATS	American thoracic society
AUC	Area under the concentration-time curve
BD	Bronchodilator
BP	Blood pressure
BTR	Best test report
BMI	Body mass index
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Observed maximum concentration
CompEx	Composite endpoint for severe exacerbations of asthma
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CRS	Chronic rhinosinusitis
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
DBP	Diastolic blood pressure
DKD	Diabetic kidney disease

Abbreviation or special term	Explanation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
E/D	Early study intervention discontinuation
EDN	Eosinophil derived neurotoxin
ERS	European Respiratory Society
FDA	Food and Drug Administration
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GCP	Good clinical practice
GINA	Global Initiative for Asthma
GGT	Gamma-glutamyl transferase
GMP	Good manufacturing practice
HbA1c	Haemoglobin A1c
HBsAg	Hepatitis B surface antigen
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
IEC/IRB	Institutional Ethics Committee/Institutional Review Board
IFN	Interferon
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
IL	Interleukin
ILC2s	Type 2 innate lymphoid cells
IMP	Investigation medicinal product
ITT	Intent-to-treat
LABA	Long-acting beta agonist(s)
LAMA	Long-acting muscarinic antagonist(s)
LTBI	Latent tuberculosis infection

Abbreviation or special term	Explanation
LTRA	Leukotriene receptor antagonist(s)
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody(ies)
mRNA	Messenger RNA
NCI	National Cancer Institute
NIMP	Non-investigation medicinal product
NOAEL	No observed adverse events level
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
OCS	Oral corticosteroid(s)
PC_{20}	Provocative concentration causing a 20% decline in FEV
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PHL	Potential Hy's law
PI	Principal Investigator
PNV	Predicted normal value(s)
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
CCI	[redacted]
RTSM	Randomisation and trial supply management
SABA	Short-acting bronchodilator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SGRQ	St George's respiratory questionnaire
SID	Subject identification
SNOT-22	Sino-nasal outcome test
SNP	Single nucleotide polymorphism
SOA	Schedule of activities
SOC	Standard of care
sST2	Soluble ST2
SV	Study visit

Abbreviation or special term	Explanation
TB	Tuberculosis
TBL	Total bilirubin
Th	T-helper
TNFα	Tumor necrosis factor alpha
TSLP	Thymic stromal lymphopoietin
ULN	Upper limit of normal
VAS	Visual analogue scale

Appendix K Protocol Amendment History

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

Amendment 3.0 (25 May 2021)

Overall Rationale for the Amendment:

Changes from Global Protocol Amendment 2.0

The principal reason for this amendment is to amend the study design to separate the main study (Part A) from the airway hyperresponsiveness and remodelling study, Part B, which was previously a sub-study.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Table of objectives and endpoints divided into 3 separate tables to present those objectives specific to Part A, Part B, and both Part A and Part B, respectively.	To add clarity to the presentation of study objectives and endpoints in the protocol.	Non-substantial
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	For Part B endpoints: added new timepoint (Week 12 compared with baseline) for FEV_1% reversibility and post BD FEV_1 (L); specified timepoints of Week 16 compared with baseline for proportion of participants who achieve at least one doubling concentration improvement in methacholine PC_{20} and Week 12 compared with baseline for 50% reduction in post BD FEV_1 reversibility.	To amend study endpoints as appropriate for the change to a 2-part study design.	Non-substantial
Section 1.1 Synopsis, Section 4.1 Overall Design	Added details of the design of Part B: approximately 44 evaluable participants to be randomised in a 1:1 ratio to receive CC mg MEDI3506 or placebo CCI by SC injection for a total of C C doses.	To amend the study design to divide it into 2 parts: Part A (main study) and Part B (airway hyperresponsiveness and remodelling study).	Substantial
Section 1.1 Synopsis, Section 9.1 Statistical Hypotheses, Section 9.2 Sample Size Determination,	Added details for Part B of sample size calculation and analysis of primary and secondary endpoints.	To specify the statistical methods for Part B.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.4 Statistical Analyses			
Section 1.3 Schedule of Activities, Section 4.1 Overall Design, Section 8.1.7 VitaloJAK Cough Monitor, Section 8.1.8.2 Cough Visual Analogue Scale, Section 8.1.9 Methacholine Challenge Testing, Section 8.1.10 Inspiratory/Expiratory Computed Tomography	Clarification added that the exploratory cough sub-study applies to Part A only, that Part B comprises the exploratory airway hyperresponsiveness and remodelling study, and that SV3 only applies to Part B.	To take into account the change to a 2-part study design.	Non-substantial
Section 1.3 Schedule of Activities, Section 4.1 Overall Design	Specified that for Part A and Part B at SV1, post-BD spirometry is to be performed if documented evidence of asthma is not already available. In Part A at SV2 it should be performed if documented evidence of asthma is not already available and in Part B at SV2 it is to be performed regardless of availability of documented evidence.	To take into account the change to a 2-part study design.	Non-substantial
Section 1.3 Schedule of Activities	Clarified that on days when investigational product is administered, all assessments should be performed pre-dose unless otherwise specified.	For clarity.	Non-substantial
Section 1.3 Schedule of Activities	For Part B, specified that echocardiogram may be performed any time after signing informed consent.	To ensure that results are available prior to methacholine challenge testing and CT scan.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 Schedule of Activities, Section 5.1 Inclusion Criteria, Section 6.2.2.1 Treatment Administration	Updated wording regarding pregnancy testing in female participants.	To ensure clarity on pregnancy testing.	Non-substantial
Section 1.3 Schedule of Activities	Clarified provision for airwave oscillometry and in-clinic spirometry to be performed 4 hours post-administration of study intervention at SV4 (Randomisation).	To add clarity for timing of pre- and post-dose airwave oscillometry and in-clinic spirometry assessments.	Non-substantial
Section 1.3 Schedule of Activities	In Part B, methacholine challenge testing and inspiratory/expiratory CT moved from SV9 to SV10. Added provision that in-clinic spirometry post-BD for Part B is at SV9, and for Part A is at SV10.	The creation of a separate study Part B (rather than a sub-study) removed logistical constraints, meaning that methacholine challenge testing and inspiratory/expiratory CT can now occur at SV10.	Non-substantial
Section 1.3 Schedule of Activities	Specified that the mean value of each parameter from the triplicate ECG will be used as the baseline value.	For clarity.	Non-substantial
Section 1.3 Schedule of Activities, Section 2.3.1 Risk Assessment	Clarified that methacholine challenge testing and CT scans will only be performed in Part B.	To specify potential risks of clinical significance that are applicable to Part B only.	Non-substantial
Section 2.3.1.1 Study Conduct During COVID-19 Pandemic	Specified that respiratory testing at locations other than the primary study site may be required in Part B of the study; consequently, participants in Part B could be at increased risk for exposure to individuals with COVID-19.	To specify the impact of the COVID-19 pandemic on Part B. AstraZeneca recognises that conduct of Part B is very challenging during the acute pandemic phase; therefore, it will be activated only when safe and feasible.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.2.1 Rationale for Endpoints	Added rationale for the Part B primary endpoint (change in methacholine PC_{20}). Clarified that objective cough monitoring will only be performed in the Part A exploratory cough sub-study.	To add rationale for the Part B primary endpoint and clarify those exploratory endpoints that apply only to Part A.	Non-substantial
Section 4.3 Justification for Dose	Clarified that the MEDI3506 dose of CC mg SC CCI will be used in Part A and Part B but the lower dose of CCI mg CCI SC will only be used in Part A.	To specify which part of the study each dose of MEDI3506 will be used.	Non-substantial
Section 5 Study Population	Section restructured to present inclusion and exclusion criteria in the following order: those applicable to both Part A and Part B, those applicable to Part A only, and those applicable to Part B only. As a consequence, some renumbering of inclusion criteria has occurred.	To provide clarification and aid sites to apply study inclusion and exclusion criteria appropriately for Part A and Part B.	Non-substantial
Section 5.2 Exclusion Criteria	Clarification of a positive IGRA test in the context of treated latent TB infection	To avoid exclusion of participants who have been treated for latent TB infection but still have a positive IGRA test	Non-substantial
Section 5.1.1, Criteria to be Assessed at SV1, Section 5.1.2, Criteria to be Assessed at SV2 and SV4 (Randomisation), Section 5.1.3 Criteria to be Assessed for Exploratory Airway Hyperresponsiveness and Remodelling Sub study, Section 5.2.1 Criteria to be Assessed at SV1 and SV2, Section 5.2.2 Criteria to be Assessed at SV1, SV2 and SV4 (Randomisation)	Section headings revised to reflect change in structure from specifying criteria at specific SVs to specifying criteria applicable to both Part A and Part B, Part A only, and Part B only.	As a consequence of restructuring the study population section.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 5.1.4 Criteria to be Assessed for Exploratory Cough Sub-study, Section 5.2.3 Criteria to be Assessed for Exploratory Airway Hyperresponsiveness and Remodelling Sub study at SV2 and SV3	Sections removed and criteria moved to relevant restructured sections.	As a consequence of restructuring the study population section.	Non-substantial
Section 5.1 Inclusion Criteria	Inclusion criterion regarding documented history of ≥ 1asthma exacerbation in 12 months prior to SV1 to be applicable to Part A only.	To avoid negatively affecting recruitment, as asthma in participants who meet this criterion may be too severe for methacholine challenge testing in Part B.	Non-substantial
Section 5.1 Inclusion Criteria	For Part B: clarified that inclusion criterion regarding morning pre-BD FEV_1 is ≥ 60% predicted normal and > 1.5 L at SV1 and SV2. Clarified that methacholine PC_{20} ≤ 8 mg/mL at SV2 serves as documented evidence of asthma.	As a consequence of the change to a 2-part study design and restructuring of the study population section.	Non-substantial
Section 5.2 Exclusion Criteria	Exclusion Criterion 23(i) updated to specify that systemic corticosteroids within 4 weeks of SV1 is allowed if use is as stable maintenance therapy for asthma.	To correct an error in protocol whereby stable maintenance therapy was permitted by Inclusion Criterion 5 (now Inclusion Criterion 4) but prohibited by the original wording of Exclusion Criterion 23	Non-substantial
Section 6.2.2.2 Monitoring Dose Administration	Stated that assessment of injection site reactions after administration of study intervention will be carried out by the blinded study team.	To clarify that the personnel who perform the assessment will be blinded to study treatment.	Non-substantial
Section 6.3.1 Methods for Assigning Treatment Groups	Added details of stratification according to study part and sub-study participation.	To take into account the change to a 2-part study design.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.3.3 Methods for Unblinding, Section 9.4 Statistical Analyses, Section 9.5 Interim Analyses	Specified, separately for Part A and Part B, timing of the primary analysis, sponsor staff unblinding, and unblinding of all personnel involved with the study analysis.	To take into account the change to a 2-part study design.	Non-substantial
Section 6.5.3 Medication Withhold Periods	Updated list of medication withhold periods to be applied prior to scheduled spirometry, AO, and FeNO measurement and added list of medication withhold periods to be applied prior to methacholine challenge testing.	For clarity and to align medication withhold periods prior to methacholine challenge testing with ERS 2017 MCT guidelines.	Non-substantial
Section 6.5.5 COVID-19 Vaccination	Updated the list of information to be recorded (if available) if and when a participant receives a COVID-19 vaccination.	To ensure collection of all data that may be needed to assess potential interaction between COVID-19 vaccine and MEDI3506.	Non-substantial
Section 8.3.10.1 Maternal Exposure, Section 8.3.10.2 Paternal Exposure, Appendix B 2 Definition of Serious Adverse Events	Changed “congenital abnormality” to “congenital anomaly”.	To align with the latest AstraZeneca Clinical Study Protocol template, in which this change was made to align with regulatory requirements.	Non-substantial
Section 8.5.2 Pharmacokinetics	Specified that samples from participants who receive placebo may be analysed to confirm no dosing with MEDI3506.	For clarification.	Non-substantial
Section 8.5.3 Immunogenicity Assessments	Specified that ADA samples may be tested for neutralising antibody.	For clarification.	Non-substantial
Section 9.4.5.2 Exploratory Biomarker Outcomes	Specified that change from baseline in EDN and total IgE will be analysed for Part A only.	Measurement in Part A only is considered sufficient.	Non-substantial
Section 9.6 Data Monitoring Committee	Reference to Study D9180C00001 changed to Study D9180C00002.	To correct an error	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.	Non-substantial

ADA = anti-drug antibody(ies); AO = airwave oscillometry; BD = bronchodilator; COVID-19 = coronavirus disease 2019; CT = computed tomography; ECG = electrocardiogram; EDN = eosinophil derived neurotoxin; ERS = European Respiratory Society; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in the first second; Ig = immunoglobulin; IGRA = interferon gamma release assay; L = litre(s); MCT = methacholine challenge testing; PC_{20} = provocative concentration causing a 20% decline in FEV; CCI SC = subcutaneous; SV = study visit; TB = tuberculosis.

Amendment 2.0 (23 February 2021)

Overall Rationale for the Amendment:

Changes from Global Protocol Amendment 1.0

The principal reason for this amendment is to respond to the recent regulatory authorisations/approvals of vaccines against COVID-19 and ensure the protocol is clear with respect to them.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.3 Schedule of Activities, Section 8.1.1 In-clinic Spirometry	Added that the timing of in-clinic spirometry at randomisation visit (SV4) should be initiated between 6:00 AM and 11:00 AM.	To correct a text omission in previous version of protocol; no change to actual conduct of the spirometry assessment	Non-substantial
Section 1.3 Schedule of Activities, Section 5 Study Population, Section 8.2.7 Clinical Safety Laboratory Assessments	Added provision that during the screening period, in the event that clinical laboratory test results are not available from central laboratories, local laboratories can be used following consultation with medical monitor.	To increase flexibility for clinical laboratory testing due to practical limitations in receiving test results.	Non-substantial
Section 1.3 Schedule of Activities, Section 2.3.1.2 COVID-19 Mitigations, Section 5.2.1 Criteria to be Assessed at SV1 and SV2	Added provision that participants are permitted to continue screening if the result from the SARS-CoV-2 PCR test performed at SV1 has not been returned by SV2 or SV3, and that the test may be performed at either SV2 or SV3 or anytime on or	To increase flexibility for COVID-19 PCR testing due to practical limitations in receiving test results.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	after Day -7 such that the results are available prior to SV4.		
Section 1.3 Schedule of Activities, Section 5.1.1 Criteria to be Assessed at SV1, Section 5.1.2 Criteria to be Assessed at SV2 and SV4 (Randomisation)	Clarification that all female participants should have a pregnancy test.	To ensure clarity on testing all females for pregnancy.	Non-substantial
Section 1.3 Schedule of Activities, Section 5.2.1 Criteria to be Assessed at SV1 and SV2, Section 8.2.7 Clinical Safety Laboratory Assessments	Added provision for retesting of IGRA.	To permit retesting of participants with a positive IGRA test result, following investigator feedback. A negative IGRA test result is still required for eligibility.	Non-substantial
Section 2.3.1.3 Vaccination Against COVID-19	New section added to inform investigators of the sponsor's approach to COVID-19 vaccination in Study D9181C00001.	Provide clarification to investigators and to help ensure interpretability of safety data.	Non-substantial
Section 5.2.1 Criteria to be Assessed at SV1 and SV2	Added provision for retesting of NT-proBNP.	To permit retesting of participants with a NT-proBNP result greater than the upper limit of the laboratory reference range if this is clinically unexpected. An acceptable NT-proBNP result is still required.	Non-substantial
Section 5.1.2 Criteria to be Assessed at SV2 and SV4 (Randomisation)	Adjustment to the periods to which the adherence criteria apply.	To remove a discrepancy between the criteria and the periods used to calculate certain relevant baseline values.	Non-substantial
Section 6.3.2 Methods to Ensure Blinding	Added allowance that limited personnel that have responsibility for analysing	To facilitate in-stream analysis of PK and ADA samples.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	PK and ADA samples can have access to the randomisation schedule.		
Section 5.2.2 Criteria to be Assessed at SV1, SV2 and SV4 (Randomisation), Section 6.5.4 Prohibited Medications	Clarification that adenoviral vector vaccines are not considered live attenuated. Addition of certain restrictions on when vaccines against COVID-19 may be administered.	Provide clarification to investigators and to help ensure interpretability of safety data.	Non-substantial
Section 6.5.5 COVID-19 Vaccination, Section 8.2.1 Medical, Surgical, and Asthma History	New text added on recording COVID-19 vaccination	To clarify the need for recording of receipt of COVID-19 vaccination.	Non-substantial

COVID-19 = coronavirus disease 2019; IGRA = interferon gamma release assay; NT-proBNP = N terminal prohormone of B type natriuretic peptide; PCR = polymerase chain reaction; SV = study visit.

Amendment 1.0 (19 October 2020)

Overall Rationale for the Amendment:

Changes from Original Global Protocol

The principal reasons for this amendment are to provide a harmonised global protocol by incorporating the changes from local amendments USA-1.0 and GER-1.0, to remove the interim analysis based on FeNO data, and clarify and correct some wording issues.

The FDA requested changes to the protocol to reflect that all AEs that occur during the study should, in relation to study stopping criteria, be treated as related to study drug, unless clearly unrelated. The FDA requested additional information on study stopping criteria and a standardised toxicity grading scale to be incorporated in the individual and study stopping criteria.

The Paul-Ehrlich-Institut requested a change to the protocol to clearly state that the use of prohibited medications will lead to discontinuation and to add this point to the list of the discontinuation criteria.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis, Section 6.3.3.1 Unblinding for interim	Removal of references to the interim analysis for the study.	Changes in pipeline and clinical development timing	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
analysis, Section 9.4 Statistical Analyses, Section 9.5 Interim Analyses		made interim analysis unnecessary.	
Section 3 Objectives and Endpoints	Removal of airway volume and airway resistance CT scan measures from airway remodelling endpoint.	Airway volume and airway resistance are not provided by the vendor providing the CT scan data.	Non-substantial
Section 4.4.1 Study Stopping Criteria	New section added.	The FDA requested the addition of study stopping criteria.	Non-substantial
Section 6.2 Preparation/Handling/ Storage/Accountability of Interventions	Addition of list item #1 to the section.	To confirm that dispensation and dosing should happen on the same day of study intervention allocation in the RTSM system.	Non-substantial
Section 6.2.2 Dose Preparation Steps	Addition of 'respectively' to step 2 of the dose preparation steps.	Clarification to instructions as use of word 'separate' in the instructions is to prevent MEDI3506 and placebo being mixed in one syringe, not to prevent 2 vials of MEDI3506 being mixed in one syringe.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Reference to relatedness of SAEs as a reason to discontinue participants from the study removed and 'any SAE of ≥ Grade 4 severity' added.	To address the comment from the FDA regarding concerns on the attribution of causality of AEs to a study drug.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 7.1 Discontinuation of Study Intervention	New discontinuation criterion added.	The PEI required the addition of this discontinuation criterion.	Non-substantial
Appendix B 2 Definition of Serious Adverse Events	Severity rating scale updated from 'mild/moderate/severe' to a Grade 1 to 5 scale based on CTCAE criteria.	In order to align with the standardised toxicity grading used to assess individual study intervention discontinuation criteria.	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

AE = adverse event; CT = computerised tomography; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration; PEI = Paul-Ehrlich-Institut; RTSM = randomisation and trial supply management; SAE = serious adverse event.

Changes from local protocol amendment USA-1.0 (04 August 2020)

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis, Section 6.3.3.1 Unblinding for interim analysis, Section 9.4 Statistical Analyses, Section 9.5 Interim Analyses	Removal of references to the interim analysis for the study.	Changes in pipeline and clinical development timing made interim analysis unnecessary.	Non-substantial
Section 3 Objectives and Endpoints	Removal of airway volume and airway resistance CT scan measures from airway remodelling endpoint.	Airway volume and airway resistance are not provided by the vendor providing the CT scan data.	Non-substantial
Section 6.2 Preparation/Handling/ Storage/Accountability of Interventions	Addition of list item #1 to the section.	To confirm that dispensation and dosing should happen on the same day of study intervention allocation in the RTSM system.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.2.2 Dose Preparation Steps	Addition of 'respectively' to step 2 of the dose preparation steps.	Clarification to instructions as use of word 'separate' in the instructions is to prevent MEDI3506 and placebo being mixed in one syringe, not to prevent 2 vials of MEDI3506 being mixed in one syringe.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	New discontinuation criterion added.	The PEI required the addition of this discontinuation criterion.	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

AE = adverse event; CT = computerised tomography; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration; PEI = Paul-Ehrlich-Institut; RTSM = randomisation and trial supply management.

Changes from local protocol amendment GER-1.0 (01 October 2020)

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 1.1 Synopsis, Section 6.3.3.1 Unblinding for interim analysis, Section 9.4 Statistical Analyses, Section 9.5 Interim Analyses	Removal of references to the interim analysis for the study.	Changes in pipeline and clinical development timing made interim analysis unnecessary.	Non-substantial
Section 3 Objectives and Endpoints	Removal of airway volume and airway resistance CT scan measures from airway remodelling endpoint.	Airway volume and airway resistance are not provided by the vendor providing the CT scan data.	Non-substantial
Section 4.4.1 Study Stopping Criteria	New section added.	The FDA requested the addition of study stopping criteria.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.2 Preparation/Handling/ Storage/Accountability of Interventions	Addition of list item #1 to the section.	To confirm that dispensation and dosing should happen on the same day of study intervention allocation in the RTSM system.	Non-substantial
Section 6.2.2 Dose Preparation Steps	Addition of 'respectively' to step 2 of the dose preparation steps.	Clarification to instructions as use of word 'separate' in the instructions is to prevent MEDI3506 and placebo being mixed in one syringe, not to prevent 2 vials of MEDI3506 being mixed in one syringe.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	Reference to relatedness of SAEs as a reason to discontinue participants from the study removed and 'any SAE of ≥ Grade 4 severity' added.	To address the comment from the FDA regarding concerns on the attribution of causality of AEs to a study drug.	Non-substantial
Appendix B 2 Definition of Serious Adverse Events	Severity rating scale updated from 'mild/moderate/severe' to a Grade 1 to 5 scale based on CTCAE criteria.	In order to align with the standardised toxicity grading used to assess individual study intervention discontinuation criteria.	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

AE = adverse event; CT = computerised tomography; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration; RTSM = randomisation and trial supply management; SAE = serious adverse event.

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