Statistical Analysis Plan	
Study Code	D9181C00001
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Date	10 Jan 2023

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 (FRONTIER3)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACM	Ambulatory cough monitoring
ACQ	Asthma control questionnaire
ADA	Anti-drug antibody(ies)
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AO	Airwave oscillometry
AST	Aspartate transaminase
BD	Bronchodilator
BMI	Body mass index
BP	Blood pressure
CompEx	Composite endpoint for severe exacerbations of asthma
COVID-19	Coronavirus disease 2019
CRS	Chronic rhinosinusitis
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
DBP	Diastolic blood pressure
E/D	Early study intervention discontinuation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDN	Eosinophil derived neurotoxin
FeNO	Fractional exhaled nitric oxide
$FEF_{25-75\%}$	Forced expiratory flow at 25-75%
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GGT	Gamma-glutamyl transferase
GINA	Global Initiative for Asthma
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin

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Abbreviation or special term	Explanation
ILC2s	Type 2 innate lymphoid cells
IP	Investigational product
ITT	Intent-to-treat
L	Liter
LABA	Long-acting beta agonist(s)
LAMA	Long-acting muscarinic antagonist(s)
LTRA	Leukotriene receptor antagonist(s)
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody(ies)
MRD	minimum required dilution
mRNA	Messenger RNA
NC	Not calculable
NQ	Not quantifiable
NR	Not reportable
NS	No sample
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
OCS	Oral corticosteroid(s)
PA	Primary analysis
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PHL	Potential Hy's law
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
CCI	CCI [redacted]
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
SNOT-22	Sino-nasal outcome test
CCI	CCI [redacted]
SOA	Schedule of activities

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Abbreviation or special term	Explanation
SOC	System Organ Class
sST2	Soluble suppression of tumorigenicity 2
SV	Study visit
TBL	Total bilirubin
TSLP	Thymic stromal lymphopoietin
ULN	Upper limit of normal
URC	Unblinded review committee
VAS	Visual analogue scale

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AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	31 Aug 2022	• Rearranging of the study endpoints to mimic the CSP • Removal of text regarding airway hyperresponsiveness and remodelling (previously a sub-study); • Change to accomodate not capping randomisation of participants not included in exploratory cough sub-study solely to achieve target sample size of the sub-study; • Introduction of the 'All randomised subject' population • Additional text added about derivation rules for actual arm; • Additional text added to clarify the meaning of 'detectable serum concentration measurement post first dose' for PK population; • Analysis visit windows for parameters previously missed have been added together with the definition of the analysis phases; • Minor adjustments on imputation rules for missing data and on PK concentration data presentation; • Additional text added to clarify the derivation rules for analysis subgroups; • Adjustments on the definition of the treatment emergent adverse events (TEAE); • Clarification around AE of special interest; • Additional text added to clarify the derivation and presentation of summary statistics; • Additional text added to clarify the fixed effects to be used in the ANCOVA, MMRM and the back-up solutions in case of non-convergence;	Y	CSP amendment v1 to v4; Improvements resulting from study team discussions and reviews.

		• Additional text added to clarify the reportable results for variables log-normally distributed; • Removal of representation of lab measurements outside predefined criteria as no predefined criteria are available; • Removal of statistical analysis on methacholine challenge testing and inspiratory/ixpiratory CT imaging as no more required; • Additional text added to introduce the primary analysis; • Shift tables for minimum values of haematology and chemistry laboratories from baseline have been added; • The recovery time formula related to asthma CompEx events occurred during the intervention and follow-up combined period has been corrected due to a previous mistake; • Clarification on rolling windows of time for asthma CompEx has been added; • An additional spirometry parameter (FEF25-75%) will be explored.		
Other	10 jan 2023	• Added 4 PD biomarkers analyses (section 4.2.8.2 Analysis of blood biomarkers) • Added that also for the eosinophils the values will be log transformed prior to the analysis • Modified ECG normal ranges table	Yes	Missing 4 PD biomarkers in previous version

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

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1 STUDY DETAILS

1.1 Study objectives

Table 1 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.

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Table 1 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.*

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Table 1 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.
CCI [redacted]	CCI [redacted]
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.*

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Table 1 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 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 [redacted]; sST2 = soluble ST2; TSLP = thymic stromal lymphopoietin; VAS = visual analogue scale. *** These endpoints will not be included in the CSR**.

1.2 Study 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 standard of care.

Approximately 228 participants will be randomised in a 1:1:1 ratio to achieve 216 evaluable participants. Participants will receive CCI [redacted] mg MEDI3506, CCI [redacted] mg MEDI3506, or placebo CCI [redacted] by SC injection CCI [redacted]. The randomisation will be stratified according to sub-study participation (exploratory cough sub-study).

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. Details of the schedule of assessment (SoA) can be found in the clinical study protocol (CSP).

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1.3 Number of participants

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 in the study (approximately 76/arm).

Up to 60 participants are intended to be included in the cough sub-study (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.

2 ANALYSIS SETS

2.1 Definition of analysis sets

The following populations are defined:

Table 2 Populations for Analysis

<table>
<tr><th>Population/Analysis set</th><th>Description</th></tr>
<tr><td>All Subjects</td><td>Participants who have signed the informed consent form during screening period.</td></tr>
<tr><td>All randomised subjects</td><td>Participants who are randomised. Participants will be analysed according to their randomised treatment group.</td></tr>
<tr><td>ITT population</td><td>Participants who are randomised and receive any study intervention. Participants will be analysed according to their randomised treatment group.</td></tr>
<tr><td>As-treated Population</td><td>Participants who are randomised and receive any study intervention. Participants will be analysed according to the treatment they actually receive as follows:
<table>
<tr><th>Highest dose actually received at any visit</th><th>Actual arm</th></tr>
<tr><td>0 mg MEDI3506 (Placebo)</td><td>Placebo</td></tr>
<tr><td>> 0 mg and ≤ CCI mg MEDI3506</td><td>CCI mg MEDI3506</td></tr>
<tr><td>> CCI mg MEDI3506</td><td>CCI mg MEDI3506</td></tr>
</table>
</td></tr>
</table>

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Table 2 Populations for Analysis

Population/Analysis set	Description
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. A participant is considered as having at least one detectable serum concentration measurement post first dose if has at least one plasma concentration that is not below the LLOQ after the first dose. Participants will be analysed according to the treatment they actually receive.
Exploratory cough sub-study	Subset of the ITT population including those participants who are participating in the exploratory cough sub-study.

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 Exploratory cough sub-study population will be used to summarise sub-study specific efficacy measures. The As-treated population will be used to summarise all safety measures (AEs, ADA, laboratory tests, ECG, and vital signs). The PK population will be used to summarise PK measures.

2.2 Violations and deviations

The list of important protocol deviations (IPDs) is provided in the Protocol Deviation Plan (PDP).

In addition, any protocol deviation related to COVID-19 will be captured with the prefix "COVID-19" for CSR reporting.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General principles

3.1.1 Baseline definitions

In general, the last measurement prior to first injection of IP will serve as the baseline measurement for efficacy and safety endpoints. If Visit 4 (Day1) measurement is missing, the last non-missing value before Visit 4 (Day 1) will be used as baseline instead. If there is no result collected prior to Visit 4, then baseline value will be set to missing and will not be imputed. In the scenario where there are two assessments on Visit 4 (Day 1) prior to first dose, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline.

An exception from the general rule will be ECGs. The mean value of each parameter from the triplicate measurements at Visit 4 (Week 0) pre-dose will be used as the baseline value.

For bi-weekly summaries, such as 2-weekly mean number of night-time awakenings, 2-weekly mean daily rescue medication usage, 2-weekly mean FEV1, 2-weekly mean PEF,

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baseline would be defined as the mean from last 2 weeks (14 days) results before Visit 4 (Week 0), ie from evening of Study Day -14 to the morning of Study Day 1. If there are fewer than 10 completed days in the 14-day baseline period (where a complete day = entry from the evening AND the following morning) then baseline will be set to missing.

For CompEx analysis the mean from last 2 weeks (14 days) results before Visit 4 (Week 0) should be derived separately for morning and evening assessments. If there are fewer than 7 completed days in the 14-day baseline period (where a complete day = entry from the evening AND the following morning) then baseline for CompEx event will be set to missing. To note: PEF is expected to be collected with 3 measurements for each morning and evening assessment. The maximum value provided by the vendor (both morning and evening for the 2-weekly mean analysis and separately for the CompEx analysis) should be used to derive the baseline and any post-baseline assessments.

3.1.2 Study day

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

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

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

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

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

3.1.3 Absolute, relative and percent change from baseline

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

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

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

For variables log normally distributed, the relative change from baseline is calculated as the visit log transformed value minus the baseline log transformed value.

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

Percentage change from baseline will not be calculated for participants where the result at baseline is 0.

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3.1.4 Analysis visit and study phase windows

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

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

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

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- If more than one non-missing assessment actual dates are equidistant from the target day, the earlier assessment will be used in the analysis.
- If more then one assessment is selected (i.e. due to teste repetitions) the average for numerical values / worst case for categorical values will be used I the analysis

The visit windows for the visits following baseline are constructed in such a way that the upper limit of the interval falls half way between the two visits, rounded up to the nearest integer. The lower limit of each window will be the mean of the two adjacent planned study days +1, rounded up to the nearest integer, except for the first post-treatment visit.

Table 3 Analysis visit windows for in-clinic spirometry, FeNO, vital signs, SARS-Cov-2 PCR test, exploratory biomarkers (serum)

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV6	Week 1	Week 1	8	All assessments on or after the first administration of investigational product to Day 19
SV7	Week 4	Week 4	29	20 to 43
SV8	Week 8	Week 8	57	44 to 71
SV9	Week 12	Week 12	85	72 to 99
SV10	Week 16	Week 16	113	100 to 127
SV11	Week 20	Week 20	141	128 to 155
SV12	Week 24	Week 24	169	≥ 156

SV = Study Visit.

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For vital signs, if the selected day is a dosing day, timepoints as per SOA within the day need to be considered (ie, Baseline, Day1: post-dose, Day1: 30m, Day1: 60m, Day1: 120m, Week1, etc...).

For in-clinic spirometry pre-BD at day 1 timepoint at 4 hour post dose need also to be considered.

Table 4 Analysis visit windows for ACQ-6, haematology, coagulation parameters, serum chemistry and immunogenicity

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV6	Week 1	Week 1	8	All assessments on or after the first administration of investigational product to Day 19
SV7	Week 4	Week 4	29	20 to 43
SV8	Week 8	Week 8	57	44 to 71
SV9	Week 12	Week 12	85	72 to 99
SV10	Week 16	Week 16	113	100 to 141
SV12	Week 24	Week 24	169	≥142

SV = Study Visit.

Table 5 Analysis visit windows for SNOT-22, Airwave Oscillometry and urinalysis

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV6	Week 1	Week 1	8	All assessments on or after the first administration of investigational product to Day 19
SV7	Week 4	Week 4	29	20 to 43
SV8	Week 8	Week 8	57	44 to 71
SV9	Week 12	Week 12	85	72 to 99
SV10	Week 16	Week 16	113	≥100

SV = Study Visit.

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Table 6 Analysis visit windows for SGRQ

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV7	Week 4	Week 4	29	All assessments on or after the first administration of investigational product to Day 57
SV9	Week 12	Week 12	85	58 to 99
SV10	Week 16	Week 16	113	100 to 141
SV12	Week 24	Week 24	169	≥142

SV = Study Visit.

Table 7 Analysis visit windows for NT-proBNP assessment

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline		All assessments prior to the first administration of investigational product
SV8	Week 8	Week 8	57	All assessments on or after the first administration of investigational product to Day 71
SV9	Week 12	Week 12	85	72 to 99
SV10	Week 16	Week 16	113	100 to 141
SV12	Week 24	Week 24	169	≥142

SV = Study Visit.

Table 8 Analysis visit windows for ECGs and total IgE (serum)

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV10	Week 16	Week 16	113	All assessments on or after the first administration of investigational product to Day 141
SV12	Week 24	Week 24	169	≥142

SV = Study Visit.

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Table 9 Analysis visit windows for PGI-BR, SARS-Cov-2 serology testing, sST2 (serum), nasal mucosal sampling (mRNA), at-home cough monitoring and cough VAS

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV10	Week 16	Week 16	113	All assessments on or after the first administration of investigational product

SV = Study Visit.

Table 10 Analysis visit windows for echocardiogram

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV9	Week 12	Week 12	85	All assessments on or after the first administration of investigational product

SV = Study Visit.

Table 11 Analysis visit windows for EDN (plasma)

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product
SV7	Week 4	Week 4	29	All assessments on or after the first administration of investigational product to Day 71
SV10	Week 16	Week 16	113	72 to 141
SV12	Week 24	Week 24	169	≥142

SV = Study Visit.

Table 12 Analysis visit windows for nasal mucosal sampling (lining fluid)

Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV4	Week 0	Baseline	1	All assessments prior to the first administration of investigational product

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Protocol Visit	Week	Analysis Visit	Scheduled Study Day	Visit Window for Analysis (Days)
SV7	Week 4	Week 4	29	All assessments on or after the first administration of investigational product to Day 43
SV8	Week 8	Week 8	57	44 to 71
SV9	Week 12	Week 12	85	72 to 99
SV10	Week 16	Week 16	113	100 to 127
SV11	Week 20	Week 20	141	128 to 155
SV12	Week 24	Week 24	169	≥ 156

SV = Study Visit.

Daily at-home eDiary (e.g., PEF, pre-BD FEV1, FEV1, rescue medication usage, asthma symptom score, awakenings) will primarily be summarised and analysed as 2-weekly averages, separately. The assessment period of visit windows are defined in the below table.

Table 1 Labelling of 2-weekly periods

2-weekly period	Adjusted defined windows visit	Scheduled day
Baseline: as defined in Section 3.1.1	Baseline	1
Period 1: Evening of Day 1 – Morning of Day 15	Week 2	15
Period 2: Evening of Day 15 – Morning of Day 29	Week 4	29
Period 3: Evening of Day 29 – Morning of Day 43	Week 6	43
Period 4: Evening of Day 43 – Morning of Day 57	Week 8	57
Period 5: Evening of Day 57 – Morning of Day 71	Week 10	71
Period 6: Evening of Day 71 – Morning of Day 85	Week 12	85
Period 7: Evening of Day 85 – Morning of Day 99	Week 14	99
Period 8: Evening of Day 99 – Morning of Day 113	Week 16	113
Period 9: Evening of Day 113 – Morning of Day127	Week 18	127
Period 10: Evening of Day 127 – Morning of Day 141	Week 20	141
Period 11: Evening of Day 141 – Morning of Day 155	Week 22	155
Period 12: Evening of Day 155 – Morning of Day 169	Week 24	169

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

For bi-weekly summaries, the mean of all non-missing observations within an assigned window is calculated. If there are fewer than 10 completed days in the 14 day period (where a

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complete day = entry from the evening AND the following morning) then the analysis value will be set to missing.

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

Table 2 Study phase windows

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

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

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

Unless otherwise specified, the study phase will be mainly used for safety analysis (e.g., laboratories, adverse events) and for CompEx analysis.

3.1.5 Handling of missing data

No imputation for missing efficacy endpoints will be done. Repeated measures mixed effect model (MMRM) will be used which, in the event of missing data, uses all data that are available.

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

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

For missing ADA data, no imputation is planned.

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

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.

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

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

3.1.5.1 Imputation of partially missing AE dates

Date and time of AE are mandatory eCRF fields. No imputations are expected. In the rare cases of missing date, following rules will be applied. Completely missing AE dates are not imputed.

Partially missing AE end dates are imputed as below:

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

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

Before proceeding with the AE start date imputation, the AE end date are imputed as described above.

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

- If the day is missing and:
  - If the month and year are different from the month and year of the first dose of IP, assume 01-MMM-YYYY.

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

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

3.1.5.2 Imputation of partially missing medication dates

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

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

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

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

3.1.6 Derivation of durations

3.1.6.1 Time since Asthma diagnosis (years)

Time from asthma first diagnosis date to screening will be calculated as (date of first diagnosis of asthma minus date informed consent signed plus one) divided by 365.25.

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3.1.6.2 Age at onset of asthma (years)

Age at onset of asthma will be calculated as the age (years) at screening minus time since asthma diagnosis (Section 3.1.6.1), rounded to the below integer.

3.1.6.3 Time since Asthma symptoms started (years)

Time from asthma first symptoms date to screening will be calculated as (date of first symptoms of asthma minus date informed consent signed plus one) divided by 365.25.

3.1.6.4 Time since last exacerbation (months)

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

3.1.6.5 Duration of exposure (days)

Exposure duration is calculated only for participants in the As-treated population as the total number of days on study drug. Exposure is calculated as (the study drug last injection date plus 28 days) minus study drug first injection date plus one. If any of the first or last dates are missing or partially missing, then imputed dates will not be used, and study drug exposure is set to missing.

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

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

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

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

3.1.6.8 Time from first IP administration to death (days)

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

3.1.6.9 Time from last IP administration to death (days)

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

3.1.7 Derivation of subgroups

Following subgroups will be explored. Any participants with a missing value for the defined subgroup will be excluded from the analysis of that subgroup. Subgroups will only be explored if there is at least 20% of the total participants in that subgroup.

- Gender (male vs female);

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- Age by category (≥ 18 to < 50 vs ≥ 50 to < 65);
- Race (as entered in the eCRF);
- BMI (< 19 kg/m², ≥ 19 - < 25 kg/m², ≥ 25 - <30 kg/m², ≥ 30 kg/m²);
- Geographical region (North America [USA], South America [Argentina], Eastern Europe [Hungary, Poland], Western Europe/Rest of the World [Germany, UK, South Africa]);
- Baseline percent predicted pre-bronchodilator FEV_1 (< 60% vs ≥ 60%);
- Age of asthma onset (< median vs ≥ median);
- Number of exacerbations in last 12 months as collected in eCRF (1 vs ≥ 2);
- Smoking status at baseline (never vs former);
- Baseline total ACQ-6 (< median vs ≥ median);
- Baseline total SGRQ (< median vs ≥ median);
- Baseline ICS total daily dose (< 500 µg vs ≥ 500 µg);
- Baseline blood eosinophils (< $0.3x10^9$ L vs ≥ $0.3x10^9$ L);
- Background medication use (dual therapy vs triple therapy);
- Baseline FeNO (< 25 ppb vs ≥ 25 ppb);
- Baseline Total IgE (≤ 100 kU/L vs > 100 kU/L);
- Baseline mono or poly sensitised to allergen (IgE) (multiple allergens sensitisation vs single allergen sensitisation);
- T2 Corren (high vs low);
- T2 GINA (high vs low);
- SARS-CoV-2 PCR test (positive at any point vs never positive);
- SARS-CoV-2 Serology test (negative at baseline and positive at end of study vs all others);
- CCI [redacted]

Background medication use

Triple therapy will be defined as the combination of inhaled corticosteroids, long-acting beta-agonist and long-acting anti-muscarinic agent (ICS + LABA + LAMA). Dual therapy will be defined as ICS + LABA.

Allergen sensitisation

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For the allergen specific IgE with a qualitative (positive or negative) result, a positive result and total IgE >100 kU/L will define sensitisation. For the allergen specific IgE with a quantitative result, a result equal or greater than 1.41 kU/L and total IgE > 100 kU/L will define sensitisation.

GINA T2 cut-offs

High T2 will be defined as a baseline eosinophil count of $\geq 0.15\times10^9$ L and/or elevated baseline FeNO (≥ 20 ppb) and/or at least one allergen sensitisation at baseline.. Other cases will correspond to Low T2.

Corren T2 cut-offs

High Th2 will be defined as a baseline total IgE level of more than 100 IU/ml (100 kU/L) and a baseline eosinophil count of 0.14×10^9 L or more; low Th2 will be defined as a baseline total IgE level of 100 IU/ml (100 kU/L) or less or baseline eosinophil count of less than 0.14×10^9 L, that is any other combination of baseline IgE and eosinophil count not included in the definition of high Th2.

CCI

[redacted]

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CCI [redacted]

In addition to the pre-specified sub-group analysis, further exploratory work may be carried out using sub-group identification methodology (e.g. SIDES). This analysis will be post-hoc and not included in the delivery of TFLs.

3.2 Baseline assessments and other subject-specific characteristics

Demographic and subject characteristics, medical history and nicotine and alcohol use are collected pre-treatment as per study protocol's SoA.

3.2.1.1 Demographics and subject-specific characteristics

Demographic and subject characteristics include age, age group (≥ 18 – < 50; ≥ 50 – 65), age group for EudraCT reporting purpose (≥ 18 – < 65; ≥ 65), sex, race, ethnic group, country, height (cm), weight (kg), body mass index (BMI) (kg/m²), previous treatments containing ICS and combination of products containing ICS, asthma characteristics at baseline. Age in years will be used as provided in the IWRS (Interactive Web Response System). BMI (kg/m²) is calculated as described in Section 3.5.2.

Height, weight and BMI are allocated to the analysis visits as per Section 3.1.4. Evaluations with missing or partially missing dates cannot be imputed to any analysis visit. Only baseline values are included in the demographic and subject characteristics.

3.2.1.2 Medical history

Medical history includes disease related and relevant medical history as collected in eCRF. Disease related and relevant medical history are coded with Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher.

3.2.1.3 Prior and concomitant medication

The WHO-DD March 2022 B3 Global or later is used to classify medications by WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

The imputation method described in Section 3.1.5.2 is used in case of medication stop date partially missing. Completely missing stop date are not to be imputed. Completely missing or partially missing concomitant medication start dates are not imputed.

After the end date imputation, the medications will be classified as either prior or concomitant (but not both) according to its stop date. Prior medication is defined as any medication with a stop date prior to the first dose of IP (exclusive). Concomitant medication is defined as any medication with a stop date on or after the first dose of study drug, or any medication taken prior to study drug and that is ongoing. Medications with completely missing stop date are classified as concomitant.

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

3.2.1.4 Asthma history

The participant's asthma history will also be collected and will include questions related to the following:

- Asthma first diagnosed date;
- First appearance of asthma symptoms date;
- Most recent exacerbation date;
- Number of asthma exacerbations within previous 12 months prior to screening (including exacerbations resulted in non-emergency room treatment, emergency room treatment, hospitalization).

3.2.1.5 Substance usage

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

3.3 Derivation of primary variable

The primary efficacy variable is the pre-bronchodilator (BD) forced expiratory volume in the first second (FEV_1) (L). Pre-BD FEV_1 (L) will be measured by in-clinic spirometry at visits SV1, SV2, SV4, SV6, SV7, SV8, SV9, SV10, SV11, SV12 and E/D. The primary efficacy endpoint is the change from baseline to Week 16 in pre-BD FEV_1 (L).

3.4 Derivation of secondary variables

3.4.1 Pharmacokinetics (PK)

Serum samples will be collected for measurement of serum concentrations of MEDI3506 at visits SV4, SV6, SV7, SV8, SV9, SV10, SV11, SV12 and E/D. Additional details are provided in Section 3.1.5.

3.4.2 Immunogenicity (serum)

Blood samples for determination of anti-drug antibodies (ADA) in serum will be assessed at visits SV4, SV6, SV7, SV8, SV9, SV10, SV12 and E/D.

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3.4.2.1 ADA definitions

ADA detection at sample level:

- A sample is considered to be ADA positive if the titre is greater than or equal to the minimum required dilution (MRD) of the assay.
- A sample is considered to be ADA negative if the titre is <MRD of the assay.

ADA detection at participant level:

- A participant is considered ADA positive if at least one collected sample is tested positive at any time during the study, including baseline and/or post-baseline (see definition for ADA prevalence in Section 3.4.2.2).
- A participant is considered ADA negative if collected samples are tested negative at all timepoints, including baseline and post-baseline.

Subjects with a missing baseline ADA assessment should be assumed to be ADA negative as a conservative approach to ensure that all subjects are included in all analyses.

Treatment-related ADA development at participant level:

Treatment-emergent ADA positive (TE-ADA+) is defined as being either of treatment-induced ADA positive (ADA negative at baseline and at least one post-baseline ADA positive) and treatment-boosted ADA positive (ADA positive at baseline and baseline titre is boosted by greater than the variability of the assay (ie ≥ 4-fold increase) at ≥ 1 post-baseline timepoint). Treatment-emergent ADA negative (TE-ADA-) is defined as ADA positive but not fulfilling the definition of TE-ADA positive.

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

3.4.2.2 Categories of ADA responses

Baseline is defined as the last ADA assessment prior to the first dose of investigational product (IP).

Numbers and proportions of:

- Participants who are ADA positive at any time during the study, including baseline and/or post-baseline (also generally referred to as ADA positive). The proportion of ADA-positive participants in a population is known as ADA prevalence.
- Participants who are ADA negative at all assessments, including baseline and post-baseline (also generally referred to as ADA negative).
- Participants who are ADA positive at baseline only.
- Participants who are ADA positive at baseline and at least one post-baseline assessment.

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- Participants who are treatment-emergent ADA positive (see definition in Section 3.4.2.1), reported overall and separately as treatment-induced and treatment-boosted subjects. The percentage of TE-ADA+ participants in a population is known as ADA incidence.
- Participants who are treatment-emergent ADA negative (see definition in Section 3.4.2.1).
- Participants who are persistently ADA positive, which is defined as ADA negative at baseline and having at least 2 post-baseline ADA positive measurements with ≥ 16 weeks between first and last positive, or an ADA positive result at the last available post baseline assessment.
- Participants who are transiently ADA positive, defined as ADA negative at baseline and at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- Participants who are ADA positive with maximum titre > median of maximum titres.

3.4.3 Asthma control questionnaire-6 (ACQ-6)

The questionnaire will be completed using the eDiary in accordance with the SoA of the CSP.

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. If response to any of the questions is missing, the ACQ-6 score will be missing. 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 key outcome variable for the ACQ-6 will be the change in mean score from baseline to Week 16. The change in mean score from baseline to each of the post-randomisation assessments will also be derived (see Section 3.1.3).

Other variables based on ACQ-6 to report include:

- Proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16 (Yes=1/No=0):
  - Yes: change from baseline ACQ-6 score to ACQ-6 score at Week 16: ≤ -0.5.
  - No: change from baseline ACQ-6 score to ACQ-6 score at Week 16: > -0.5.
- Proportion of participants achieving ACQ-6 well controlled status (Yes=1/No=0):
  - Yes: ACQ-6 score at Week 16 ≤ 0.75.
  - No: ACQ-6 score at Week 16 > 0.75.

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Participants with missing or non-evaluable ACQ-6 score will be considered as not achieving ACQ-6 response.

3.4.4 St George's respiratory questionnaire (SGRQ)

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

The SGRQ will be completed using the eDiary in accordance with the SoA of the CSP, and a 4 week recall version will be used.

The key outcome variable for the SGRQ will be the change in mean total and domain scores from baseline to Week 16, but the change in mean total and domain scores from baseline to each of the post-randomisation assessments will also be derived (see Section 3.1.3).

Other variables based on SGRQ to report include:

- Proportion of participants with a decrease in SGRQ score of ≥ 4 points from baseline to Week 16 (Yes=1/No=0):
  - Yes: change from baseline SGRQ score to SGRQ score at Week 16: ≤ -4.
  - No: change from baseline SGRQ score to SGRQ score at Week 16: > -4.

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

3.4.5 Post-BD FEV_1

Secondary efficacy variable is the post-BD FEV_1 and will be measured by in-clinic spirometry at visits SV1, SV2, SV4, SV8 and SV10. The secondary endpoint is the absolute change from baseline to Weeks 8 and 16 in post-BD FEV_1 (L) (see Section 4.2.5).

3.4.6 Asthma CompEx

Asthma CompEx is a combination of exacerbations of asthma and diary events (ie, combination of eDiary variables). Asthma CompEx is a composite surrogate endpoint for exacerbations of asthma, recently developed by AstraZeneca (it is not yet a regulatory-approved clinical endpoint).

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Diary events are defined by the threshold and slope criteria using the following morning/evening (AM/PM) diary variables:

- PEF (variable 1=V1= morning PEF; variable 2=V2= evening PEF).
- Symptom score (0 – 3) (variable 5=V5= morning symptom score; variable 6=V6= evening symptom score).
- Use of rescue medication (variable 3=V3= morning rescue medication usage; variable 4=V4= evening rescue medication usage).

A subject will be considered to have a CompEx event if the subject has one or both of the following:

1 An asthma exacerbation,

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

For this purpose, "2 consecutive days" means strictly the same 2 consecutive days when assessing multiple requirements within those days. For the eDiary data (which is captured twice during the day), one day will be defined by the morning/evening pairing for consistency with published precedent for the CompEx endpoint. (Note: other eDiary endpoints in this trial will use an evening/morning pairing to define one day.) The morning eDiary recordings captured on the first day of treatment will not be included in the calculation of the CompEx endpoint.

Threshold criterion:

(a) ≥15% decrease from baseline in either morning (V1) or evening home-based PEF (V2),

and at least one of the following:

(b) ≥1.5 doses increase from baseline in rescue medication in either the morning (for preceding night, V3) or evening (for preceding day, V4),

(c) ≥1 score increase from baseline, or the absolute maximal symptom score, in either the morning (V5) or evening (V6).

For (b), the number of doses of rescue medication is defined as the number of puffs of inhaler recorded in the morning and evening, respectively.

For (c), the asthma symptom score (scored 0-3) as described in Section 3.6.2.1 (V1-V6), provided those non-missing values meet the criterion.

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Slope criterion:

One of (a), (b) or (c) above is met for ≥2 consecutive days *and* the regression slope requirement over the preceding 5 days is also met.

The regression slope requirement in the preceding 5 days is that all of the following are met:

- Morning PEF slope ≤ -3%/day;
- Evening PEF slope ≤ -3%/day;
- Morning (preceding night) rescue medication slope ≥ 0.3 doses/day;
- Evening (preceding day) rescue medication slope ≥ 0.3 doses/day;
- Morning asthma symptom score slope ≥ 0.2 score/day;
- Evening asthma symptom score slope ≥ 0.2 score/day.

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the absolute values of each of the six variables (V1-V6) separately against day number, with no other variables included in the regression model.

For morning and evening PEF, the regression slope thus obtained will first also be divided by the baseline PEF value before applying the above criterion. The following table shows how the timing for the 5-day requirement for the regression slopes fits with the 2-consecutive day requirement, where "Day 0" here refers to the first of the 2 consecutive days (shaded) to be used each time the rolling 2 consecutive day assessment is made:

Table 3 Timing for assessment of CompEx slope criterion

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

A regression slope will be calculated provided there are at least two non-missing values in the required 5 days. If one or more of the six variables above (V1-V6) does not have at least two non-missing values in the required 5 days, then the slope requirement therefore cannot be met.

The start date of a CompEx event is defined as the earliest of the exacerbation or objective deterioration start dates which meets the definition. Diary event start date is defined as the earliest Day 0 (in notation from Table 15) from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criterion.

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The end date of a CompEx event is defined as the latest of the exacerbation or objective deterioration end dates which meets the definition. Diary event end date is defined as the latest Day 1 (in notation from Table 3 Timing for assessment of CompEx slope criterion) from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criterion.

The event duration is defined as the end date minus the start date plus 1.

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

For CompEx analyses, only on-treatment events (based on the period from baseline to last dose date +28 days) will be considered. A supplementary analysis including events in the period from baseline to end of follow-up (Week 24) will also be conducted.

Time-to-first event will be defined as: [Start date of first event or censoring – date of 1st dose] + 1.

Date of first event will be the first start date of a CompEx event as defined above. For participants who do not experience an on-treatment CompEx event, date of censoring will be the minimum between the date of last dose plus 28 days, and the last day of eDiary recording during the on-treatment period. For the analysis of CompEx during combined treatment and follow-up period, date of censoring will be the minimum between the date of end of study visit, and the last day of eDiary recording during combined treatment and follow-up period .

For recurrent events, there must be a gap of 7 days between events ie, at least 7 days between end date of first CompEx event and start date of second CompEx event. Events that occur closer in time will be collapsed into one event.

The time during the event and the 7 days after each event will not be considered when defining time at risk for the CompEx event rate. Time at risk will be defined as [Date of last treatment plus 28 days– date of 1st dose] + 1 – recovery time. For the analysis of CompEx during combined treatment and follow-up period, the time at risk will be defined as [date of end of study visit – date of 1st dose] + 1 – recovery time.

The annualised rate of asthma CompEx events, during intervention period (Baseline to last dose date +28 days) per participant will be calculated as:

Annualised rate of asthma CompEx events during intervention period =

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$$\frac{\text{Total number of asthma CompEx events}}{(\text{Date of last dose of IP} + 28 - \text{Date of the first dose of IP} - \text{recovery time} + 1)/365.25}$$

where the recovery time is defined as:

$$\sum_{i=1}^{k}[min(i^{th}\ event\ end\ date + 7, date\ of\ last\ dose + 28) - i^{th} event\ start\ date + 1]$$

The annualised rate of asthma CompEx events, during intervention and follow-up periods (Baseline to Week 24) per participant will be calculated as:

Annualised rate of asthma CompEx events during intervention and follow-up periods =

$$\frac{\text{Total number of asthma CompEx events}}{(\text{Date of last follow up} - \text{Date of the first dose of IP} - \text{recovery time} + 1)/365.25}$$

Where the recovery time is defined as:

$$\sum_{i=1}^{k}[min(i^{th}\ event\ end\ date + 7, date\ of\ last\ follow\ up) - i^{th} event\ start\ date + 1]$$

Rolling windows of time:

The deterioration criteria for the individual diary variables are defined as a combination of threshold criteria and regression slope criteria during each rolling window. Each rolling window contains 6 consecutive days, including 2 consecutive days for threshold assessment (Window Day 0 and 1), and 5 preceding consecutive days for regression slope assessment (Window Day -4 to 0). For this purpose, "2 consecutive days" means the same 2 consecutive days when assessing multiple threshold requirements. Similarly, '5 preceding consecutive days' means the same 5 preceding consecutive days when assessing multiple slope requirements.

Rolling Window	Study Day	1	2	3	4	5	6	7	8	……	n	n+1	n+2	n+3	n+4	n+5
1	**Window Day**	-4	-3	-2	-1	0	1									
	Threshold Assessment					x	x									
	Slope Assessment	x	x	x	x	x										
2	**Window Day**		-4	-3	-2	-1	0	1								

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Rolling Window	Study Day	1	2	3	4	5	6	7	8	……	n	n+1	n+2	n+3	n+4	n+5
	Threshold Assessment						x	x								
	Slope Assessment		x	x	x	x	x									
3	**Window Day**			-4	-3	-2	-1	0	1							
	Threshold Assessment							x	x							
	Slope Assessment			x	x	x	x	x								
……																
n	**Window Day**										-4	-3	-2	-1	0	1
	Threshold Assessment														x	x
	Slope Assessment										x	x	x	x	x	

The deterioration criteria are assessed for a series of rolling windows over the entire study duration. For example, Window 1 includes 'Study Day 1' through 'Study Day 6', Window 2 rolls one day forward that includes 'Study Day 2' through 'Study Day 7', Window 3 rolls one day forward that includes 'Study Day 3' through 'Study Day 8', and so on so forth, as illustrated in the table below:

Table 46 Rolling windows of time

3.4.7 Fractional Exhaled Nitric Oxide (FeNO)

Percent change from baseline to Week 16 in concentration of FeNO in exhaled breath is a secondary endpoint of this study. Additionally, percent and relative change from baseline to Weeks 1, 4, 8, 12, 16, 20, and 24 will be analysed as exploratory endpoints.

Airway inflammation will be evaluated using a standardised single-breath FeNO test at visits SV1, SV2, SV4, SV6, SV7, SV8, SV9, SV10, SV11, SV12 and E/D. Two acceptable FeNO measurements will be performed to establish repeatability; up to 8 measurements can be performed. The mean value of the measurements, as provided by the vendor, will be used in the statistical analysis. Percent and relative change from baseline in FeNO will be derived in accordance with Section 3.1.3 of this SAP.

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3.5 Derivation of safety variables

3.5.1 Adverse events (AEs)

AEs will be collected from signing of ICF throughout the intervention period and including the follow-up period. SAEs will be recorded from the time of signing of ICF. AEs will be coded with MedDRA version 25.0 or higher.

AE data will be allocated to the study phase (as defined in section 3.1.4) according to their onset date. AEs will be defined as treatment emergent adverse events (TEAEs) if they have an onset, during the on-treatment phase. AEs with a missing start date will be considered as on-treatment.

3.5.1.1 Adverse events of special interest

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 of the protocol.
- 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.
- Gastrointestinal adverse events.
- Malignancy.

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

3.5.2 Vital signs variables

Vital signs assessments (body temperature, diastolic blood pressure (DBP), systolic blood pressure (SBP), heart (pulse) rate and respiratory rate) will be performed at visits SV1, SV4, SV6, SV7, SV8, SV9, SV10, SV11, SV12 and E/D. For SV4 and SV7 vital signs will be taken before and immediately after administration of study intervention, and at 30, 60, and 120

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minutes (± 5 minutes). For SV8 and SV9 vital signs will be taken before and immediately after administration of study intervention, and at 30 and 60 minutes (± 5 minutes) thereafter.

Height will be assessed at SV1 only. Weight will be assessed at SV1, SV4, SV10, SV12 and E/D.

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

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

Table 17 Vital sign reference ranges

Parameter	Standard Unit	Lower limit	Upper limit	Change Criteria
Body temperature	°C		>37	±1
DBP	mmHg	<60	>100	±15
SBP	mmHg	<90	>160	±30
Heart (pulse) rate	beats/min	<50	>100	±20
Respiratory rate	breath/min	<12	>24	±3
BMI	kg/m²	<18.5	≥35	

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

3.5.3 Laboratory variables

Clinical Safety Laboratory will be performed at visits SV1, SV4, SV6, SV7, SV8, SV9, SV10, SV12 and E/D, except for urinalysis that will be performed at visits SV1, SV4, SV6, SV7, SV8, SV9, SV10 and E/D. Clinically significant abnormal laboratory results are defined by the investigator.

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

Table 18 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

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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 of the protocol.
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.

3.5.3.1 Other safety tests

- NT-proBNP (only at SV1, SV8, SV9, SV10, SV12 and E/D)
- SARS-CoV-2 PCR test (performed anytime between Day -7 and Day -4 as the results are needed prior to randomisation. Testing may then be performed at any point during the study intervention and follow-up periods for a participant suspected of having COVID-19)

3.5.3.2 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 SV4, SV10 and E/D.

3.5.4 Electrocardiogram (ECG)

ECG variables will be collected at visits SV1, SV4, SV10, SV12, and E/D as follows:

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

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- PR interval
- QT interval

Additionally, QT correction using Bazett's and Fridericia's formulas will be calculated as follows (unless already derived directly from the CRF):

QTcB = QT/(RR^½),

QTcF = QT/(RR^⅓),

where QT is measured in msec and RR is measured in sec.

Categorical ECG interpretation (normal, abnormal clinically significant, abnormal not clinically significant) will be provided by the investigator.

Table 19 ECG reference ranges

Parameter	Standard Unit	Lower limit	Upper limit	Change criteria
Heart (pulse) rate	beats/min	<50	>100	
RR interval	ms	<600	>1200	
QRS interval	ms	<80	>120	
PR interval	ms	<120	>200	
QT interval	ms	N/A	>450 male >470 female	+30
QTcB interval	ms	N/A	>450 male >470 female	+30
QTcF interval	ms	N/A	>450 male >470 female	+30

3.5.5 Echocardiogram

A transthoracic echocardiogram to assess left ventricular ejection fraction (LVEF) will be assessed any time after signing of informed consent, so that results are available prior to randomisation and then at any time at or between SV9 and SV10 inclusive.

3.6 Derivation of exploratory variables

3.6.1 Airwave oscillometry (AO) variables

Airwave oscillometry will be performed at SV2, SV4, SV6, SV7, SV8, SV9 and SV10. Airwave oscillometry is a non-invasive lung function test included in this study to evaluate treatment effect on small airway physiology.

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The parameters R5, R20, 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.

3.6.2 Patient reported outcome (PRO) variables

Patient-reported outcome data will be captured via an ePRO device. For all outcomes based on the ePRO devices, analyses will be based on data up to and including Week 24.

For asthma symptom score, rescue medication use and home peak expiratory flow, 2-weekly means will be calculated. A 2-weekly mean is calculated as the sum of all non-missing daily measures/scores over 14 sequential days divided by the number of days with non-missing measures/scores. For nights with awakenings due to asthma, the 2-weekly mean will be the percentage of times the participant answered "yes" to 'did your asthma cause you to wake up' and "yes" to 'did you use rescue medication upon awakening'. For derivation of the 2-weekly mean scores see Section 3.1.4. Note that the first 2-weekly mean in the treatment period will be based on the evening recording on day 1 up to and including the morning recording on day 15. The daytime score is recorded in the evening and the night-time score is recorded the following morning; 2-weekly periods are defined as follows (where Day 1 is the day of randomisation)

Where a total score is calculated within a day (e.g. Asthma symptom score), this calculation will span two calendar days – the daytime value recorded in evening of day X, and the night-time value recorded on morning of day x+1. E.g. the asthma symptom score on Day 1 will be the day time score recorded on the evening of Day 1 + the night-time score recorded on the morning of Day 2.

Where only night-time scores/results are of interest, the morning entries on the second day of a period up to and including the morning entry on the last day of the period (or morning of the last day of study for the last period/last IP intake) will be considered. Where only daytime scores/results are of interest, the evening entries on the first day of the period up to and including the evening entry on the second last day of the period (or evening before the last day of study/last IP intake) will be considered.

3.6.2.1 Asthma symptom score

Asthma symptoms during night-time and daytime will be recorded by the participant each morning and evening in the asthma daily diary. Each symptom item will be recorded using a scale 0 – 3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning), and total score will be calculated and presented separately.

The daily asthma symptom total score will be calculated by taking the sum of the daytime and night-time asthma symptom scores recorded each day. If a participant is missing a value for

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either night-time or daytime asthma symptom score on a given day, then the total score for that day will be set to missing.

The outcome variable is the change from baseline through Week 24 in 2-weekly mean daily asthma symptom total score. 2-weekly means and change from baseline for daytime and night-time scores will also be calculated for the 2-weekly periods according to Table 1 (Section 3.1.4).

3.6.2.2 Rescue medication usage

During the study period, participants will be required to document rescue medication usage in the eDiary twice daily. Daytime use is recorded in the evening and night-time use is recorded in the morning.

The outcome variable is the 2-weekly mean daily rescue medication usage (puffs/day) and will be calculated for the 2-weekly periods according to Table 1 (Section 3.1.4).

3.6.2.3 Nights with awakening due to asthma

Bi-weekly mean change from baseline in the number (percentage) of nights with awakening due to asthma that required rescue medication will be calculated as the outcome variable for the 2-weekly periods according to Table 1 (Section 3.1.4).

3.6.2.4 Home FEV_1

Bi-weekly mean absolute changes from baseline home FEV_1 will be calculated for the 2-weekly periods according to Table 1 (Section 3.1.4).

3.6.2.5 Home peak expiratory flow (morning and evening)

Bi-weekly mean absolute changes from baseline PEF will be calculated for the 2-weekly periods according to Table 1 (Section 3.1.4).

3.6.3 FEV_1% reversibility and FEF25-75%

Exploratory variable are the FEV_1% reversibility and FEF25-75%. They will be measured by in-clinic spirometry at visits SV1, SV2, SV4, SV8 and SV10. Reversibility is calculated as follows:

$$FEV_1\%\ \text{reversibility} = (\text{post-BD } FEV_1 - \text{pre-BD } FEV_1)/\text{pre-BD } FEV_1 \times 100$$

The exploratory endpoint is the change from baseline to Weeks 8 and 16 in FEV_1% reversibility and FEF25-75%.

3.6.4 Asthma exacerbation

Asthma exacerbation will be assessed throughout the duration of the study.

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Time to first asthma exacerbation will be calculated as start date of asthma exacerbation minus date of 1st dose plus 1.

The annualised rate of asthma exacerbation during intervention period (Baseline to last dose date +28 days) per participant will be calculated as:

$$\text{Annualised exacerbation rate during intervention period} = \frac{No.of\ exacerbations}{(Date\ of\ last\ dose\ of\ IP\ +\ 28\ -\ Date\ of\ 1st\ dose - recovery\ time +\ 1)\ /\ 365.25}$$

The annualised rate of hospitalised asthma exacerbation during intervention period per participant will be calculated as:

$$\text{Annualised hospitalised exacerbation rate during intervention period} = \frac{No.of\ exacerbations\ which\ resulted\ in\ hospitalisation}{(Date\ of\ last\ dose\ of\ IP\ +28\ -\ Date\ of\ 1st\ dose - recovery\ time +\ 1)\ /\ 365.25}$$

The recovery time is defined as:

$$\sum_{i=1}^{k}[min(i^{th}\ exacerbation\ end\ date + 7, date\ of\ last\ dose\ of\ study\ intervention + 28) - i^{th}\ exacerbation\ start\ date + 1]$$

3.6.5 Patient Global Impression of Benefit/Risk (PGI-BR)

The PGI-BR is a 5-item questionnaire assessing the participant's perception of the overall benefits and risks of treatment at SV10. 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.

3.6.6 Asthma related inflammatory blood biomarkers

Asthma related inflammatory blood biomarkers will be assessed at visits SV1, SV4, SV7, SV8, SV9, SV10, SV11, SV12 and E/D and will include following parameters:

- plasma EDN
- total IgE
- sST2
- Allergen-specific IgE

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3.6.7 Sino-nasal Outcome Test-22 (SNOT-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 sino-nasal 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 of the CSP. The exploratory endpoint will be the change from baseline through Week 16 in SNOT-22.

3.7 Derivation of exploratory cough sub-study variables

Objective cough measurements

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 SV2 and SV10. The digitally recorded data will be sent to Vitalograph who will undertake cough counting for all participants using a standardised process. Following parameters will be provided:

- Daily cough frequency.
- Awake time cough frequency.
- Night-time cough frequency.

All frequency data will be recorded to two decimal places. The minimum recording time for the measurement to be 'done' is 1 hour, however the minimum recording time required for analysis is 18 hours within the 24-hour interval, and subjects' data with recording time < 18 hours will be excluded from analysis.

Cough VAS

Participants will be asked to complete a cough severity VAS (100 mm linear scale marked with a horizontal line by the participant, with 0 mm representing ''no cough'' and 100 mm representing "worst cough") measuring subjective assessment by the participant of the prior 24 hours for severity of cough symptoms (Smith et al 2006). Exploratory endpoint will be the change from baseline to Week 16 in cough VAS.

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4 ANALYSIS METHODS

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 Database 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.

4.1 General principles

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

Treatment groups will be displayed as follows:

- MEDI3506 CCI mg
- MEDI3506 CCI mg
- Placebo

The standard descriptive summary statistics for a set of continuous data are n, mean, standard deviation, median, minimum value and maximum value. Other summary statistics (e.g., standard error (SE) least-squares mean (LSmean), confident interval (CI)) may be suitable in addition. For log transformed data geometric mean and coefficient of variation (CV) will be presented in addition to the standard descriptive summary statistics. Concentration data will be summarised using descriptive statistics, including n, n<lower limit of quantification, arithmetic mean, arithmetic standard deviation (SD), geometric mean, coefficient of variation (CV%), geometric mean -/+ geometric SD (gSD), minimum, median, and maximum values. The geometric mean is calculated as the exponential of the arithmetic mean calculated from data on a natural log scale. The geometric CV% is calculated as 100 x sqrt[exp(s^2)-1], where s is the SD of the data on the natural log scale. The geometric mean -/+ gSD is calculated as exp(mean(log(PK Conc)) -/+ std(log(PK Conc))).

For continuous data the mean, median, geometric mean, first quartile (Q1), third quartile (Q3), LSmean, CI, SD and SEwill be rounded to 1 additional decimal place compared to the analysed data. Minimum and maximum will be displayed with the same accuracy as the analysed data. Coefficient of variation (CV%), where reported, will always be reported to 1 decimal place.

For categorical data, percentages will be rounded to 1 decimal place.

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PK concentration descriptive statistics will all be presented as follows:

- Arithmetic mean, arithmetic SD, geometric mean, geometric CV%, Geometric Mean -/+ gSD, median: 4 significant figures
- Minimum, maximum: 3 significant figures
- Data listing: same significant figures as supplied from bioanalysis.

The primary analysis will be performed after all participants have completed SV10 (Week 16) or have withdrawn from the study. At the time of the primary analysis all data collected on and prior to data cut-off date (i.e., Week 16 visit date for the last subject) will be cleaned. For the purpose of the statistical analysis, data cut-off rules might be implemented and described in a separate document.

All data collected until the time of the final DBL will be included in the final analysis. No cut-off rules will be implemented for the final analysis.

4.1.1 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:

- H_0: Change from Baseline in FEV_1 at Week 16 (MEDI3506-placebo) = 0.
- H_1: 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 CCI mg versus placebo in regard to H_0
- Step 2: If previous step rejects: test MEDI3506 CCI mg versus placebo in regard to H_0

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4.1.2 Repeated measures mixed effects analysis of covariance model (MMRM)

The repeated measures mixed effects analysis of covariance model (MMRM) will be used to fit change from baseline for continuous endpoints at each visit, for the ITT population. The model will include all available data from all visits up to and including the target visit, 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, background medication use, geographic region, baseline ICS total daily dose, visit, treatment and the baseline by visit and treatment by visit interactions. Visits within subject are considered as repeated measurements. An unstructured covariance matrix will be used to describe the correlations between observations on a participant between visits. The denominator degrees of freedom will be calculated using the Kenward-Rogers method. In the event that the model with unstructured covariance matrix fails to converge, an autoregressive (1) covariance matrix will be used instead. If also the autoregressive (1) does not converge, a compound symmetry covariance matrix will be used. If the model still does not converge, the baseline by visit effect will be deleted from the model. Estimates of the least square mean change from baseline in endpoint variable for each treatment, and the difference between them, together with two-sided 80% confidence interval, will be obtained from the model for each visit. The significance of the treatment effect will be tested at a 10% one-sided level of significance as described in Section 4.1.1.

The reportable results from the model will be:

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

If the dependent variable is considered to be normally distributed, the variable fitted in the model will be the change from baseline; the MMRM and the reportable results will be those described above.

On the other hand, if the dependent variable is considered to be log-normally distributed, the variable fitted in the model will be the change from baseline in logarithmical scale, with the logarithm of the baseline value as a covariate. Change from baseline in logarithmic scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

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

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- For the percent change:
  - Back transformed LSmeans for each group, which correspond to the estimated percent change from baseline; back transformed LSmeans is derived as [EXP(LSMean)-1]*100;
  - Two-sided 80% CI of the back transformed LSmeans for each group; 80% CI of the back transformed LSmeans is derived as [EXP(Lower limit of the 80% CI of the LSmean)-1]*100; [EXP(Upper limit of the 80% CI of the LSmean)-1]*100;
- For the relative change:
  - Back transformed LSmeans for each group, which correspond to the estimated relative change from baseline; back transformed LSmeans is derived as EXP(LSMean);
  - Two-sided 80% CI of the back transformed LSmeans for each group; 80% CI of the back transformed LSmeans is derived as EXP(Lower limit of the 80% CI of the LSmean); EXP(Upper limit of the 80% CI of the LSmean);
- For the comparison:
  - The estimated geometric LSMean ratio between active groups and placebo; the ratio is calculated as EXP(LSMean difference);
  - The Two-sided 80% CI of the ratio; the 80% CI of the ratio is calculated as EXP(Lower limit of the 80% CI of the LSmean difference)0; EXP(Upper limit of the 80% CI of the LSmean difference);
  - One-sided p-value.

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

The MMRM will be applied using PROC MIXED (SAS procedure).

4.1.3 Analysis of covariance (ANCOVA)

An ANCOVA model will be used to analyse change from baseline for continuous endpoints collected at only one post-baseline visit. The treatment group will be considered as a fixed effect of the model, with the baseline value, background medication use, geographic region and baseline ICS total daily dose as covariates. Comparisons of MEDI3506 CCI mg versus placebo and MEDI3506 CCI mg versus placebo will be assessed within the same model. The restricted maximum likelihood (REML) approach will be used for the estimation of the variance and covariance parameters of the linear model; one-sided difference test, with alpha level at 10% will be used for the treatment comparisons. No imputation will be made for missing data.

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The reportable results from the model will be:

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

If the parameter results to be normally distributed, the variable fitted in the model will be the change from baseline; the ANCOVA model and the reportable results will be those described above.

On the other hand, if the parameter results to be log-normally distributed, the variable fitted in the model will be the change from baseline in logarithmical scale. Change from baseline in logarithmical scale is defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value.

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

- For the percent change:
  - Back transformed LSmeans for each group, which correspond to the estimated percent change from baseline; back transformed LSmeans is derived as [EXP(LSMean)-1]*100;
  - Two-sided 80% CI of the back transformed LSmeans for each group; 80% CI of the back transformed LSmeans is derived as [EXP(Lower limit of the 80% CI of the LSmean)-1]*100; [EXP(Upper limit of the 80% CI of the LSmean)-1]*100;
- For the relative change:
  - Back transformed LSmeans for each group, which correspond to the estimated relative change from baseline; back transformed LSmeans is derived as EXP(LSMean);
  - Two-sided 80% CI of the back transformed LSmeans for each group; 80% CI of the back transformed LSmeans is derived as EXP(Lower limit of the 80% CI of the LSmean); EXP(Upper limit of the 80% CI of the LSmean);
- For the comparison:
  - The estimated geometric LSMean ratio between active groups and placebo; the ratio is calculated as EXP(LSMean difference);
  - The Two-sided 80% CI of the ratio; the 80% CI of the ratio is calculated as EXP(Lower limit of the 80% CI of the LSmean difference)0; EXP(Upper limit of the 80% CI of the LSmean difference);
  - One-sided p-value.

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4.1.4 Chi-squared test

The chi-square test will be used to assess the difference in proportion of responders. The difference between active treatment groups versus placebo will be presented with the two-sided 80% confidence intervals the one-sided p-values.

4.1.5 Negative binomial regression

Negative binomial regression will be used for the analysis of event rates. In this study the response variable in the model will be the number of asthma CompEx events, the number of asthma exacerbations, or the number of hospitalised asthma exacerbations experienced by a participant. The model will include treatment group, background medication, geographic region and baseline ICS total daily dose as covariates. The logarithm of the participant's corresponding follow-up time will be used as an offset variable in the model to adjust for participants having different exposure times during which the events occur.

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

The estimated annualised event rate in each group, the estimated treatment effect (ie, the rate ratio of each treatment group versus placebo), corresponding two-sided 80% CI, and one-sided p-value for the rate ratio will be presented. The estimate of the negative binomial overdispersion parameter will also be reported.

4.1.6 Cox proportional hazards

Time to first asthma CompEx event/ first asthma exacerbation data will be analysed using Cox proportional hazard model including treatment group, background medication, geographic region and baseline ICS total daily dose as covariates. Results of the analysis will be summarised as hazard ratios, two-sided 80% confidence intervals and one-sided p-values. Time to first asthma CompEx event/ asthma exacerbation will be displayed graphically using a Kaplan-Meier plot.

4.2 Analysis of variables

4.2.1 Disposition of subjects

Subject dispositions (number and percentage of participants enrolled, participants randomised, participants not randomised (incl. reasons), participants who received at least one dose of study IP, participants who did not receive treatment, participants who completed the treatment, participants who did not complete treatment (incl. reasons), participants who completed the study and participants withdrawn from study (incl. reasons)) will be presented in a summary table for each treatment group and overall. A listing including all standardized disposition terms will be also provided for all discontinued subjects. The table will be based

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on 'All Subjects' population and repeated for the ITT population. The listing will be based on the ITT population.

The number of participants belonging to each analysis population will be presented in a summary table by treatment group and overall. Listing of all participants excluded from any analysis set will be also provided. The listing will include reason for exclusion from respective.

The number and percentage of subject recruitment by region and country will be presented for the ITT population.

The number and percentage of participants with one or more disruption due to COVID-19 pandemic will be presented by treatment group and overall. A listing of all participants affected by the COVID-19 related study disruption , and a description of how the individual's participation was altered, will be produced. COVID-19 related study disruptions can be:

- Visit related (if visit is impacted by global/country situation, then contact mode will be specified);
- Study drug related (if study drug administration or location was impacted by global/country situation; who performed a study drug administration);
- Concomitant medication related (if when treatment was stopped due to any global/country related situations ie: epidemic/pandemic, healthcare crisis etc.);
- Withdrawal from study (if primary reason for ending study is related to global/country situation).

Participants with reported issues in the clinical trial management system due to COVID-19 will be listed.

Randomisation scheme and codes as well as subjects receiving the various batch of investigational product will be listed.

Number and percent of participants remaining on treatment, discontinued treatment but still in study, and participants withdrawn from the study at each scheduled visit will be summarised. Participants completing the study will be listed.

Number and percentage of participants in sub-study will be summarised for the ITT population.

4.2.2 Important protocol deviations

The number and percentage of participants with at least one IPD, including COVID-19 related IPD, will be summarised based on the categories specified in the Protocol Deviation Plan (PDP), for each treatment group and overall.

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All IPDs will be also listed based on the ITT population. All issues reported due to COVID-19 pandemic, regardless of whether the type of issue is considered a protocol deviation or not, will be listed separately (see Section 4.2.1).

4.2.3 Baseline assessments and other subject-specific characteristics

4.2.3.1 Demographics and subject-specific characteristics

All demographic and subject-specific characteristics reported in section 3.2.1.1 will be presented in summary tables for each treatment group and overall; age, height, weight and BMI will be summarised descriptively; all the other demographic and subject-specific characteristics will be summarised as categorical variables with the number and percentages of participants by categories. Only the baseline measurement for height, weight and BMI will be considered.

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

4.2.3.2 Medical history

Medical history as described in section 3.2.1.2 will be presented in summary tables as number and percentages of participants by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall. Participants with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Participants with events in more than one SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted alphabetically by SOC and PT. The tables will be based on the ITT population.

4.2.3.3 Prior and concomitant medication

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

A separate table will be presented for participants who take disallowed concomitant medications, excluding ICS and ICS containing medications. Percentages will be calculated relative to the number of participants in the ITT population.

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

4.2.3.4 Asthma history

Asthma characteristics at baseline (age at asthma onset (Section 3.1.6.2), time since asthma diagnosis (Section 3.1.6.1), time since asthma symptoms started (Section 3.1.6.3), time since last asthma exacerbation (Section 3.1.6.4), total number of asthma exacerbations within previous 12 months prior to screening, including exacerbations resulted in non-emergency room treatment, emergency room treatment, hospitalization (Section 3.2.1.4)) will be summarised by treatment and overall for the ITT population. Descriptive summary statistics

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will be produced for previous and concomitant treatments containing ICS and combination of products containing ICS. Asthma characteristics at baseline and previous and concomitant treatments containing ICS and combination of products containing ICS will also be listed for the ITT population.

4.2.3.5 Substance usage

Summary statistics will be produced by substance usage category (never, former, current), by treatment group and overall, for alcohol and tobacco use (as specified in Section 3.2.1.5) for the ITT population. Additionally, descriptive statistics on the number of pack-years for former or current cigarettes smokers will be provided.

4.2.3.6 Other assessments at Screening

Summary statistics for eDiary data at baseline such as 2-weekly mean PEF, 2-weekly mean FEV1, number of days with awakening and rescue medication use, number of days with rescue medication used during the night and number of days with rescue medication use during the day, will be provided by treatment and overall.

4.2.4 Analysis of primary efficacy endpoint

4.2.4.1 Primary analysis of the primary endpoint

The primary efficacy endpoint is the change from baseline in pre-BD FEV_1 to Week 16.

The primary estimand is a 'Treatment Policy' estimand, as follows: The difference in mean change from baseline in pre-BD FEV_1 at Week 16 (MEDI3506 – placebo) will be analysed using MMRM (see Section 4.1.2) 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. Graphical representations of the LSMean change from baseline and the two-sided 80% CI over time will be provided by treatment group using the ITT population.

The observed values and change from baseline through Week 16 in pre-BD FEV_1 (L) by treatment group and visit will be summarised using the ITT population.

4.2.4.2 Supportive analysis of the primary endpoint

As a supportive analysis of the primary endpoint, the MMRM analysis (see Section 4.1.2) will be repeated on the ITT population using data from visits up to and including Week 16, but excluding the data from visits after IP discontinuation. Graphical representations of the LSMean change from baseline and the two-sided 80% CI over time will be provided by treatment group using the ITT population.

4.2.4.3 Subgroup analysis for the primary endpoint

For each of the subgroup factors (see Section 3.1.7) a separate MMRM will be fitted using the same covariates as described for the primary analysis in Section 4.2.4.1. Geographical region

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will not be a covariate if it is the subgroup; baseline ICS total daily dose will not be a covariate if it is the subgroup; background medication will not be a covariate if it is the subgroup. MMRM results from subgroup analysis will be displayed using forest plot.

The observed values and change from baseline through Week16 pre-BD FEV_1 (L) by treatment group, visit and subgroup will be summarised using the ITT population.

4.2.4.4 Exploratory analysis of the primary endpoint

The exploratory analysis of the primary analyses will consist of the following.

The primary analysis will be repeated on the ITT population using data from visits up to and including Week 16 by means of the MMRM as described in section 4.1.2, CCI [redacted]

Additionally, the exploratory analysis of the primary endpoint will consist of repeating the MMRM analysis (see Section 4.1.2) on the ITT population from visits up to and including Week 24.

Graphical representations of the LSMean change from baseline and the two-sided 80% CI up to and including Week 24 will be provided by treatment group using the ITT population.

The observed values and absolute change from baseline though Week 24 will be summarised by treatment group using the ITT population.

4.2.5 Analysis of secondary endpoints

4.2.5.1 Analysis of lung function parameters measured in clinic

The observed values and changes from baseline in lung function parameters measured in clinic such as pre-BD FEV_1, post-BD FEV_1 , FVC, FEV_1/FVC, percent predicted FEV_1, percent predicted FVC, PEF and FEF25-75% will be summarised by treatment group and visit for the ITT population. Observed values and changes from baseline in pre-BD FEV_1 to 4-hours post administration of IP at Day 1 will also be summarised.

The difference in mean change from baseline in post-BD FEV_1 to Weeks 8 and 16 will be estimated using a MMRM, similar to that described for the primary efficacy analysis (Section 4.1.2). The change from baseline through Week 16 will be included in the model. LSMean change from baseline and two-sided 80% CI through Week 16 in post-BD FEV_1 will be presented in figures.

All lung function parameters measured in clinic will be also reported in listing using the ITT population.

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4.2.5.2 Analysis of ACQ-6

Change from baseline to Week 16 in ACQ-6 will be analysed using MMRM (see Section 4.1.2). LSMean change from baseline and two-sided 80% CI through Week 24 in ACQ-6 score will be presented in figures.

Observed values and absolute change from baseline through Week 16 will be summarised by treatment group using the ITT population.

As a part of exploratory analysis change from baseline through Week 24 in ACQ-6 will also be analysed.

Number and proportion of participants with a decrease in ACQ-6 score of ≥ 0.5 from baseline to Week 16 and number and proportion of participants achieving ACQ-6 well controlled status at Week 16 (as defined in Section 3.4.3) will be summarised and analysed using chi-squared test as described in Section 4.1.4 for the ITT population.

A listing including results from each of the questions and the ACQ-6 score will be produced for the ITT population.

4.2.5.3 Analysis of SGRQ

Change from baseline to Week 16 in SGRQ total and domain scores will be analysed using MMRM (see Section 4.1.2). LSMean change from baseline and two-sided 80% CI through Week 16 in SGRQ total score will be presented in figures.

Observed values and absolute change from baseline through Week 16 will be summarised.

As a part of exploratory analysis change from baseline through Week 24 in SGRQ total score will also be analysed.

Number and proportion of participants with a decrease in SGRQ total score of ≥ 4 points from baseline to Week 16 (as defined in Section 3.4.4) will be summarised and analysed using chi-squared test as described in Section 4.1.4 for the ITT population.

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

4.2.5.4 Analysis of Asthma CompEx

Time to first asthma CompEx event will be analysed using a Cox proportional hazard model, with group, background medication, geographic region and baseline ICS total daily dose as covariates (see Section 4.1.6). All available data from participants through Week 16 will be included. Additionally, the analysis of time to first asthma CompEx event will be repeated using all available data from participants through Week 24 (end of follow-up).

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Time to first asthma CompEx will also be displayed in a Kaplan-Meier plot, including all data through to Week 24 (end of follow-up).

The asthma CompEx event rate will be analysed using negative binomial regression, with the log(follow-up time) included as an offset term and treatment group, geographic region, baseline ICS total daily dose as covariates (see Section 4.1.5). The dependent variable will be the number of asthma CompEx events through Week 16. All available data from participants through to Week 16 will be included, irrespective of whether they discontinued study intervention.

Additionally, the analyses of the asthma CompEx event rate will be repeated using all available data from participants through Week 24 (end of follow-up).

Asthma CompEx events will be also reported in listing for the ITT population.

4.2.5.5 Analysis of FeNO

Relative and percent change from baseline through 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 4.1.2 – reportable results for variables log-normally distributed). Estimates of the least square mean change from baseline for each treatment, and the difference between them, together with two-sided 80% confidence interval and one-sided p-values, will be obtained from the model for each visit. LSMean percent change from baseline through Week 16 in concentration of FeNO will be presented in figure. Observed concentration of FeNO and relative and percent change from baseline will be descriptively summarised for the ITT population.

As a part of exploratory analysis change from baseline through Week 24 in concentration of FeNO will also be analysed.

FeNO results will be also reported in listing for the ITT population.

4.2.6 Analysis of exploratory endpoints

4.2.6.1 Analysis of AO

Change from baseline in AO parameters (R5, R20, R5-R20, AX) will be analysed using MMRM (see Section 4.1.2). LSMean change from baseline and two-sided 80% CI for each visit through Week 16 in AO parameters will be presented in figures.

Observed values and change from baseline through Week 16 will be descriptively summarised for all AO parameters by treatment groups for the ITT population.

AO parameters will be also reported in listing for the ITT population.

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4.2.6.2 Analysis of FEV1% reversibility and FEF25-75%

The difference in mean change from baseline in FEV_1 % reversibility (see Section 3.6.3) through Week 16 will be estimated using a MMRM, similar to that described for the primary efficacy analysis (Section 4.1.2). The change from baseline through Week 16 will be included in the model.

The FEF25-75% will also be analysed in the same way.

4.2.6.3 Analysis of asthma exacerbation

Time to first asthma exacerbation will be analysed using a Cox proportional hazard model, with treatment group, geographic region and baseline ICS total daily dose as covariates (see Section 4.1.6). The data will also be displayed in a Kaplan-Meier plot.

Number of exacerbations, total follow-up time and annual exacerbation rate including the two-sided 80% CI will be summarised by treatment group for the ITT population. Asthma exacerbations during the intervention period (baseline to last dose date +28 days) will be analysed using negative binomial model (see Section 4.1.5). Rate ratio from MEDI3506 CCI mg compared to placebo and from MEDI3506 CCI mg compared to placebo will be displayed. Similarly, the hospitalised asthma exacerbations will also be analysed.

Asthma exacerbations and hospitalised asthma exacerbations will be also reported in listing for the ITT population.

4.2.6.4 Analysis of PGI-BR

The results of the 5-item questionnaire of the PGI-BR will be descriptively summarised at Week 16 by treatment group for the ITT population.

PGI-BR responses will be also reported in listing.

4.2.6.5 Analysis of SNOT-22

The total SNOT-22 score and the change from baseline will be descriptively summarised by visit andby treatment group for the ITT population.

Total SNOT-22 score as well as single questions will be also reported in listing for the ITT population.

Change from baseline through Week 16 in SNOT-22 score will be analysed using MMRM (see Section 4.1.2). LSMean change from baseline and two-sided 80% CI through Week 16 in SNOT-22 score will be presented in figures.

4.2.6.6 Analysis of diary data and home spirometry

2-weekly mean asthma symptom score, 2-weekly mean rescue medication usage, 2-weekly mean night time awakening due to asthma, 2-weekly mean home FEV_1 and 2-weekly mean

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home PEF as derived in Section 3.6.2 through Week 24 and the changes from baseline through Week 24 will be descriptively summarised using the ITT population.

Additionally, change from baseline will be analysed using MMRM (see Section 4.1.2). The LSmean changes from baseline and two-sided 80% CI through Week 24 will be presented in figures.

2-weekly means will be also reported in listing for the ITT population.

4.2.7 Analysis of safety endpoints

Duration of exposure as calculated in Section 3.1.6 will be summarised by treatment groups for the As-treated population.

CCI [redacted]

Number and percentage of participants who received planned starting dose, who received different starting dose from planned, who had any interruption or 1, 2, 3, etc. interruption will be summarised by treatment group for the As-treated population. Reason for interruption will also be provided.

Interruption will be defined as any administration where action taken is reported as 'Drug interrupted'.

A listing of the administration of investigational product together with the duration of exposure will be presented for all subjects belonging to the As-treated population.

4.2.7.1 Analysis of AEs

All AE summary tables and listings will be created by treatment group and for total MEDI3506 for the As-treated population, unless otherwise specified. AEs occurred during study intervention (on-treatment phase as defined in section 3.1.4) and follow-up period (follow-up phase as defined in section 3.1.4) will be reported in summary tables. All AEs, including AEs for enrolled but not randomised participants and for participants who were not exposed to treatment, will be listed.

An overall summary table will be produced by treatment group and for total MEDI3506 showing the number and percentage of participants with at least one AE in any of the following categories:

- AEs;
- AEs with toxicity grade 4 or 5;
- Serious adverse events (SAEs);

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- Deaths due to AE;
- AEs leading to discontinuation of IP;
- AEs leading to dose interruption;
- AEs leading to withdrawal from study;
- AESI.

The total number of AEs in the different AE categories in terms of AE counts (ie, accounting for multiple occurrences of the same event in a subject) will also be presented by treatment group and for total MEDI3506.

Number and percentage of participants with at least one AE by SOC term will be produced by treatment group and for total MEDI3506.

Number and percentage of participants with at least one AE by PT will be produced for AEs with a frequency of > 5% by treatment group and for total MEDI3506. Frequency will be defined according to percentage in total MEDI3506.

Number and percentage of participants with AE by SOC and PT will be summarised by treatment group and for total MEDI3506.

Number and percentage of participants with AE by PT and maximum reported toxicity grade will be summarised by treatment group and for total MEDI3506 in table and AEs with frequency of >5% per treatment group will be graphically displayed using bar graphs. Each participant is represented only for the maximum reported intensity of each PT. Frequency will be defined according to percentage in total MEDI3506.

Number and percentage of participants with AEs by PT and investigator's causality assessment will be summarised by treatment group and for total MEDI3506.

Total number of AEs by SOC and PT will be summarised by treatment group and for total MEDI3506. Total number of SAEs by SOC and PT will be summarised by treatment group and for total MEDI3506.

Number and percentage of participants with AE leading to dose interruption by SOC and PT will be summarised by treatment group and for total MEDI3506.

Number and percentage of participants with non-serious AEs and number of non-serious events occurring in more than 5% of participants will be summarised by SOC and PT.

Number and percentage of participants with AE with outcome of death by SOC and PT will be summarised by treatment group and for total MEDI3506. Key subject information for

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participants experience AEs with outcome of death will be produced for each treatment group using following information:

- Treatment group
- Subject identifier
- Sex
- Age (years)
- Event term as reported by the investigator
- PT
- Time from first IP administration to onset of AE (days) as derived in Section 3.1.6.6
- Treatment period
- Time from last IP administration to death (days) as derived in Section 3.1.6.9
- Time from first IP administration to death (days) as derived in Section 3.1.6.8
- Received treatment for AE
- Reasonable possibility AE caused by IP

Number and percentage of participants with SAE by SOC and PT will be summarised by treatment group and for total MEDI3506. Key subject information for participants experience SAEs will be produced using following information:

- Treatment group
- Subject identifier
- Sex
- Age (years)
- Event term as reported by the investigator
- PT
- Time from first IP administration to onset of AE (days) as derived in Section 3.1.6.6
- Time from last IP administration prior to AE start date, calculated for AEs starting after the discontinuation of the IP.
- Time from start of IP administration to becoming serious
- Outcome
- Action taken with IP
- Reasonable possibility AE caused by IP.

Number and percentage of participants with AE leading to discontinuation of IP by SOC and PT will be summarised by treatment group and for total MEDI3506. Key subject information for participants experience AEs leading to discontinuation of IP will be produced using following information:

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- Treatment group
- Subject identifier
- Sex
- Age
- AE as reported by the investigator
- PT
- Time from first IP administration to AE onset
- Time from first IP administration to discontinuation of IP
- Seriousness
- Outcome
- Reasonable possibility AE caused by IP.

Number and percentage of participants with AESIs by maximum reported toxicity grade will be summarised by treatment group and for total MEDI3506. A list of PTs for AESIs experienced during the study will be produced. Number of participants with injection site reaction (ISR) by maximum reported toxicity grade will be summarised by treatment group and for total MEDI3506.

Number of subjects with COVID-19 related AESIs by maximum reported toxicity grade will be summarised by treatment group and for total MEDI3506. Similar table will be repeated for the number of subjects with COVID-19 related serious AESIs.

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

4.2.7.2 Analysis of vital signs

Observed values and change from baseline in vital signs will be summarised by treatment group and for total MEDI3506, and visit. Key subject information will be produced for vital sign parameters treatment-emergent changes outside predefined criteria (Table).

Individual vital sign results will be listed.

4.2.7.3 Analysis of laboratory measurements

Laboratory evaluations (haematology, clinical chemistry and quantitative urinalysis parameters as per Table) will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit by treatment group and for total MEDI3506. Categorical haematology, clinical chemistry and urinalysis results will be summarised in shift tables comparing maximum value during treatment with baseline value by treatment group and for total MEDI3506. Similarly, haematology and clinical chemistry results will also be summarised in shift tables comparing minimum value during treatment.

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ALT or AST versus total bilirubin, expressed as multiples of ULN as well as liver biochemistry test results over time – participants with elevated ALT or AST, and elevated total bilirubin at any point during the study following the start of study medication will be presented in figures.

In addition to the summaries above also the maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's law criteria will be presented by treatment group and for total MEDI3506.

All laboratory results will be listed as well as any SARS-CoV-2 test results.

4.2.7.4 Analysis of ECG

ECG variables will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit by treatment group and for total MEDI3506. Investigators' ECG assessments at baseline versus last observation on treatment will be summarised in shift table by treatment group and for total MEDI3506. Key subject information will be produced for ECG parameter values outside predefined criteria (Table).

In addition, the number and percentage of participants with QTcF intervals (derived as described in Section 3.5.4) at any observation on treatment >450 ms, >480 ms, >500 ms and QTcF increase from baseline >30 ms, >60 ms, >90 ms, and combination of both, will be presented by treatment group and for total MEDI3506.

Individual ECG results and abnormalities in ECG will be listed.

4.2.7.5 Analysis of echocardiogram

Observed values and change from baseline in LVEF will be summarised by visit, by treatment group and for total MEDI3506 using descriptive summary statistics for the As-treated population.

Individual echocardiogram results and abnormalities will be listed.

4.2.7.6 Other safety tests

NT-proBNP results will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit for the As-treated population. NT-proBNP results will be also summarised in shift tables comparing maximum value during treatment with baseline value for the As-treated population.

The number of subjects tested positive for SARS-CoV-2 (by PCR or serology test) at end of study, but who were tested negative at baseline visit will also be presented.

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Finally, the number of subjects tested positive for SARS-CoV-2 (by PCR or serology test) during the study (including both intervention and follow-up periods) who experienced or not at least one COVID-19 related AEs/SAEs will be provided.

4.2.8 Other analysis

4.2.8.1 Immunogenicity and PK

Summary of ADA responses during the study with number and percentage of participants in each category (defined in Section 3.4.2.2) and ADA titres over time displaying min, Q1, median, Q3 and max, will be provided by treatment group. The impact of ADA on MEDI3506 PK concentrations will be assessed. Sumary of AEs by ADA status will be provided. The relationship between ADA and biomarkers or efficacy might be evaluated.

MEDI3506 serum concentrations will be tabulated along with descriptive statistics.

Geometric mean (together with gSD) serum MEDI3506 concentration over time will be plotted by treatment. Individual serum MEDI3506 concentration over time plots will be provided. Spaghetti plots of individual serum MEDI3506 concentrations over time by ADA category (TE-ADA negative, TE-ADA positive, ADA negative) will also be generated.

All serum concentrations data will be listed for PK population. ADA results and participants key subject information for ADA positive participants will be provided for the As-treated population.

Separately from the CSR, population PK modelling may be performed and reported, and potential correlation between PK exposure and pharmacodynamic biomarker, efficacy/safety response may be evaluated.

4.2.8.2 Analysis of blood biomarkers

Analysis of blood eosinophils

Blood eosinophils count will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit for the ITT population. Change from baseline in blood eosinophils will be analysed using MMRM as described in Section 4.1.2 for the ITT population. Endpoints will 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 two-sided 80% confidence interval and one-sided p-values, will be obtained from the model for each visit. LSMean change from baseline and two-sided 80% CI for each visit through Week 24 in blood eosinophils will be presented in figure.

Blood eosinophils count will be also summarised in shift tables comparing maximum value during treatment to baseline value for the ITT population.

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Other exploratory biomarkers

The following serum and plasma biomarkers will be collected and summarised:

- Total IgE, allergen-specific IgE, sST2 (serum);
- Plasma EDN;
- CCI [redacted]
- Serum IL-5;
- Serum IL-13;
- Serum TSLP.

Allergen-specific IgE status and Serum IL33:ST2 at baseline will be used for subgroup analysis of the primary endpoint (pre-BD FEV_1) as described in Section 4.2.4.3. The subgroup cut-off for Serum IL33:ST2 is the Serum IL33:ST2 baseline median.

All the above biomarkers, except allergen specific IgE will be summarised with descriptive statistics at each visit and change from baseline summarised for each post-baseline visit. Change from baseline in all the above biomarkers, except allergen specific IgE and Serum IL33:ST2 will be analysed using a MMRM as described in Section 4.1.2. Endpoints will be log transformed prior to analysis. LSMean change from baseline and two-sided 80% CI for each analysed visit will be presented in figures.

4.2.8.3 Exploratory analyses

Analysis of Objective Cough

Observed values, percentage and relative change from baseline to Week 16 in objective cough measurements (see Section 3.6.2) will be summarised for ITT population.

Percentage and relative changes from baseline in objective cough measures at Week 16 will be analysed using an analysis of covariance model as described in Section 4.1.3 (reportable results for variables log-normally distributed). Objective cough measurements will be log-transformed prior to analysis. LSMean change from baseline to Week 16, together with the two-sided 80% CI, in objective cough parameters will be presented in figure.

Cough VAS

Observed values and absolute change from baseline to Week 16 in cough VAS score will be summarised by visit for ITT population.

Change from baseline to Week 16 in cough VAS score will be analysed using an ANCOVA model as described in Section 4.1.3. LSMean change from baseline to Week 16, together with the two-sided 80% CI, in cough VAS score will be presented in figure.

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

5 INTERIM ANALYSIS

No formal interim analyses are planned for this study.
The primary analysis (PA) 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 PA 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.

6 CHANGES OF ANALYSIS FROM PROTOCOL

This SAP is based on study protocol D9181C00001 Amendment V4.0 dated 08 March 2022. Any further amendment of the study protocol which can have an impact on the SAP will lead to an amendment of this document. Changes of analysis from D9181C00001 Amendment V4.0 dated 08 March 2022 are listed here below:

Section 3 Objectives and endpoints

- Time to first CompEx event based on the period from baseline to Week 16 is a secondary endpoint for this study. However, in this SAP, a supplementary analysis including events on the period from baseline to end of follow-up (Week 24) has been added.
- An additional spirometry parameter not part of the main study endpoints (FEF25-75%) will be explored.

Section 8.1.8.3 Asthma Control Questionnaire-6

In this section is stated that "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". In this SAP it is specified that "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".

Section 9.4.2.1 Primary Endpoint

In this section it is stated that the MMRM will include "fixed effects for baseline, visit, treatment and the baseline by visit and treatment by visit interactions". In this SAP it is mentioned that the MMRM will additionally include background medication, geographic region and baseline ICS total daily dose as fixed effects. The same variables will be added as covariates to ANCOVA, logistic regression, Cox proportional hazards and negative binomial models.

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8 APPENDIX

Appendix A Calculation of SGRQ scores

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

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

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

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

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

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

The Total score is calculated in similar way:

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

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

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

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

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

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Sum of maximum possible weights for each component and Total (for Step 2 in calculations):

- Symptoms 662.5;
- Activity 1209.1;
- Impacts 2117.8;
- Total 3989.4.

Item weights

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

PART 1

Response	Response weight
1) Over the past 4 weeks, I have coughed:	
Almost every day	80.6
Several days a week	63.2
A few days a month	29.3
Only with respiratory infections	28.1
Not at all	0.0
2) Over the past 4 weeks, I have brought up phlegm (sputum):	
Almost every day	76.8
Several days a week	60.0
A few days a month	34.0
Only with respiratory infections	30.2
Not at all	0.0
3) Over the past 4 weeks, I have had shortness of breath:	

Response	Response weight
Almost every day	87.2
Several days a week	71.4
A few days a month	43.7
Only with respiratory infections	35.7
Not at all	0.0
4) Over the past 4 weeks, I have had wheezing attacks:	
Almost every day	86.2
Several days a week	71.0
A few days a month	45.6
Only with respiratory infections	36.4
Not at all	0.0
5) How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?	
More than three	86.7
3 attacks	73.5
2 attacks	60.3
1 attack	44.2
None	0.0
6) How long did the worst respiratory attack last?	
a week or more	89.7
3 or more days	73.5
1 or 2 days	58.8
less than a day	41.9
7) Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?	
None	93.3

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Response	Response weight
1 or 2	76.6
3 or 4	61.5
nearly every day	15.4
every day	0.0
8) If you wheeze, is it worse when you get up in the morning?	
No	0.0
Yes	62.0

PART 2

Response	Response weight
9) How would you describe your respiratory condition?	
The most important problem I have	83.2
Causes me quite a lot of problems	82.5
Causes me a few problems	34.6
Causes no problem	0.0
10) If you have ever held a job:	
My respiratory problems made me stop working altogether	88.9
My respiratory problems interfere with my job or made me change my job	77.6
My respiratory problems do not affect my job	0.0
Not applicable	
11) These are questions about what activities usually make you feel short of breath these days.	
Sitting or lying still	90.6

Response	Response weight
Washing or dressing yourself	82.8
Walking around the house	80.2
Walking outside on level ground	81.4
Walking up a flight of stairs	76.1
Walking up hills	75.1
Playing sports or other physical activities	72.1
12) These are more questions about your cough and shortness of breath these days.	
Coughing hurts	81.1
Coughing makes me tired	79.1
I am short of breath when I talk	84.5
I am short of breath when I bend over	76.8
My coughing or breathing disturbs my sleep	87.9
I get exhausted easily	84.0
13) Questions about other effects your chest trouble may have on you.	
My cough or breathing is embarrassing in public	74.1
My respiratory problems are a nuisance to my family, friends or neighbours	79.1
I get afraid or panic when I cannot catch my breath	87.7
I feel that I am not in control of my respiratory problems	90.1
I do not expect my respiratory problems to get any better	82.3
I have become frail or an invalid because of my respiratory problems	89.9
Exercise is not safe for me	75.7
Everything seems too much of an effort	84.5
14) These are questions about your respiratory treatment.	
My treatment does not help me very much	88.2

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Response	Response weight
I get embarrassed using my medication in public	53.9
I have unpleasant side effects from my medication	81.1
My treatment interferes with my life a lot	70.3
15) These are questions about how your activities might be affected by your respiratory problems.	
I take a long time to get washed or dressed	74.2
I cannot take a bath or shower, or I take a long time to do it	81.0
I walk slower than other people my age, or I stop to rest	71.7
Jobs such as household chores take a long time, or I have to stop to rest	70.6
If I walk up one flight of stairs, I have to go slowly or stop	71.6
If I hurry or walk fast, I have to stop or slow down	72.3
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	74.5
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	71.4
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	63.5
16) We would like to know how your respiratory problems usually affect your daily life.	
I cannot play sports or do other physical activities	64.8
I cannot go out for entertainment or recreation	79.8
I cannot go out of the house to do the shopping	81.0
I cannot do household chores	79.1
I cannot move far from my bed or chair	94.0
17) Now please select the response (one only) that you think best describes how your respiratory problems affect you:	

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Response	Response weight
It does not stop me from doing anything I would like to do	0.0
It stops me from doing one or two things I would like to do	42.0
It stops me from doing most of the things I would like to do	84.2
It stops me from doing everything I would like to do	96.7

Handling of missing items

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

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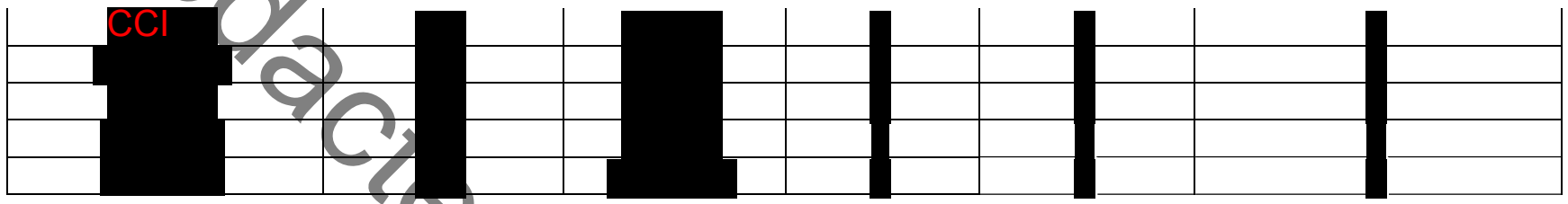

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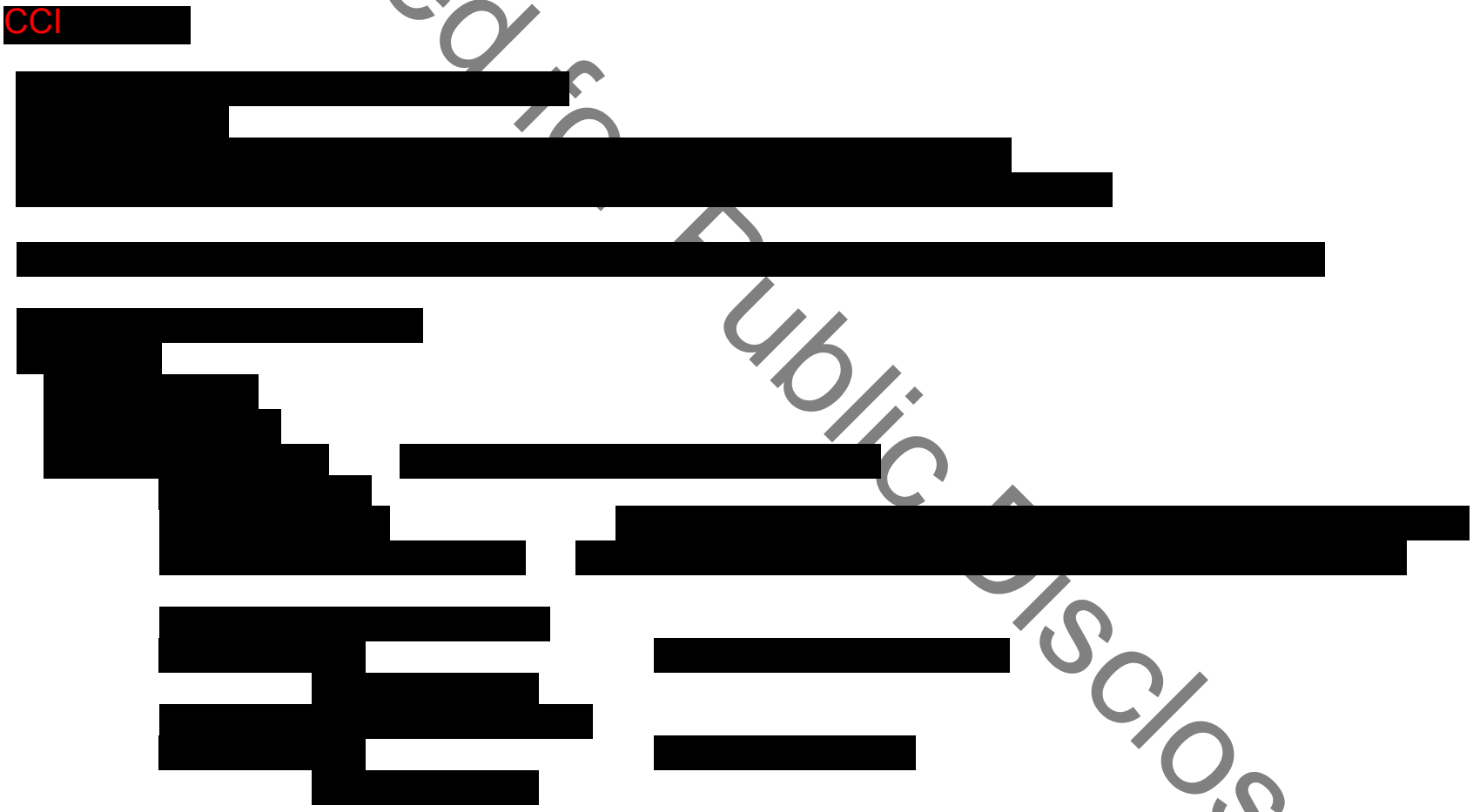

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Appendix C TFL TOC

TFL number	Title	Population
14.1 Demographic, baseline, concomitant medication and other subject-specific characteristics		
Table 14.1.1.1	Subject disposition	All subjects
Table 14.1.1.2	Subject disposition	ITT population
Table 14.1.1.3	Subject participation in sub-study	ITT population
Table 14.1.2	Important protocol deviations	ITT population
Table 14.1.3	Analysis sets	
Table 14.1.4	Subject recruitment by region and country	ITT population
Table 14.1.5	Demographic characteristics	ITT population
Table 14.1.6.1	Medical history	ITT population
Table 14.1.6.2	Prior treatments containing ICS and combination of products containing ICS	ITT population
Table 14.1.6.3	Concomitant treatments containing ICS and combination of products containing ICS	ITT population
Table 14.1.6.4	Prior medications	ITT population
Table 14.1.6.5	Disallowed concomitant medications	ITT population
Table 14.1.6.6	Allowed concomitant medications	ITT population

Table 14.1.7.1	Subject characteristics	ITT population
Table 14.1.7.2	Diary data at baseline	ITT population
Table 14.1.7.3	Asthma characteristics at baseline	ITT population
Table 14.1.7.4	Number (%) of subjects remaining on treatment, discontinued treatment but still in study and subjects withdrawn from the study at each scheduled visit	ITT population
Table 14.1.7.5	Substance use, categorised	ITT population
Table 14.1.8	Summary of COVID-19 study disruptions	ITT population
14.2 Efficacy evaluation data		
14.2 Spirometry		
Table 14.2.1.1	Lung function parameters measured in clinic by visit, summary statistics	ITT population
Table 14.2.1.2	Lung function parameters measured in clinic by visit and subgroup, summary statistics	ITT population
Table 14.2.1.3	Change from baseline to Week 16 in pre-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM	ITT population
Figure 14.2.1.1	Change from baseline through Week 16 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI)	ITT population
Table 14.2.1.4	Change from baseline to Week 16 in pre-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM - supportive analysis	ITT population

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Figure 14.2.1.2	Change from baseline through Week 16 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI) - supportive analysis	ITT population
Table 14.2.1.5	Change from baseline to Week 16 in pre-BD FEV1 (as measured in the clinic) treatment comparisons by subgroups, MMRM	ITT population
Figure 14.2.1.3	Change from baseline through Week 16 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI) by subgroups	ITT population
Figure 14.2.1.4	Change in pre-BD FEV1 measured in the clinic at Week 16, MMRM - forest plot by subgroups	ITT population
Table 14.2.1.6	Change from baseline to Week 16 in pre-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM - exploratory analysis	ITT population
Table 14.2.1.7	Change from baseline through Week 24 in pre-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM	ITT population
Figure 14.2.1.5	Change from baseline through Week 24 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI)	ITT population
Table 14.2.1.8	Change from baseline through Week 16 in post-BD FEV1 (as measured in the clinic) treatment comparisons, MMRM	ITT population
Figure 14.2.1.6	Change from baseline through Week 16 in post-BD FEV1 measured in the clinic, LSMeans (80% CI)	ITT population
Table 14.2.1.9	Change from baseline through Week 16 in FEV1% reversibility (as measured in the clinic) treatment comparisons, MMRM	ITT population

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Figure 14.2.1.7	Change from baseline through Week 16 in FEV1% reversibility measured in the clinic, LSMeans (80% CI)	ITT population
Table 14.2.1.10	Change from baseline through Week 16 in pre-BD FEF25-75% (as measured in the clinic) treatment comparisons, MMRM	ITT population
Table 14.2.2.1	Home spirometry parameters 2-weekly means, summary statistics	ITT population
Table 14.2.2.2	Change from baseline through Week 24 in 2-weekly mean PEF (measured at home) treatment comparisons, MMRM	ITT population
Figure 14.2.2.1	Change from baseline through Week 24 in 2-weekly mean PEF measured at home, LSMeans (80% CI)	ITT population
Table 14.2.2.3	Change from baseline through Week 24 in 2-weekly mean FEV1 (measured at home) treatment comparisons, MMRM	ITT population
Figure 14.2.2.2	Change from baseline through Week 24 in 2-weekly mean FEV1 measured at home, LSMeans (80% CI)	ITT population
14.2 ACQ		
Table 14.2.3.1	ACQ-6 score by visit, summary statistics	ITT population
Table 14.2.3.2	Change from baseline to Week 16 in ACQ-6 score treatment comparisons, MMRM	ITT population
Figure 14.2.3	Change from baseline through Week 16 in ACQ-6 score, LSMeans (80% CI)	ITT population
Table 14.2.3.3	Change from baseline through Week 24 in ACQ-6 score treatment comparisons, MMRM	ITT population

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Table 14.2.3.4	Proportion of subjects achieving a decrease in ACQ-6 score of >=0.5 from baseline to Week 16	ITT population
Table 14.2.3.5	Proportion of subjects achieving a decrease in ACQ-6 score of >=0.5 from baseline to Week 16 treatment comparisons chi-squared test	ITT population
Table 14.2.3.6	Proportion of subjects achieving ACQ-6 well controlled status at Week 16	ITT population
Table 14.2.3.7	Proportion of subjects achieving ACQ-6 well controlled status at Week 16 treatment comparisons chi-squared test	ITT population
14.2 SGRQ		
Table 14.2.4.1	SGRQ domains and total score by visit, summary statistics	ITT population
Table 14.2.4.2	Change from baseline to Week 16 in SGRQ domains and total score treatment comparisons, MMRM	ITT population
Figure 14.2.4	Change from baseline through Week 16 in SGRQ domains and total score, LSMeans (80% CI)	ITT population
Table 14.2.4.3	Change from baseline through Week 24 in SGRQ domains and total score treatment comparisons, MMRM	ITT population
Table 14.2.4.4	Proportion of subjects with a decrease in SGRQ total score of >= 4 points from baseline to Week 16	ITT population
Table 14.2.4.5	Proportion of subjects with a decrease in SGRQ total score of >= 4 points from baseline to Week 16 treatment comparisons chi-squared test	ITT population

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14.2 CompEx		
Table 14.2.5.1	Time to first Asthma CompEx event (days) based on the period from baseline to Week 16 - Cox-regression analysis	ITT population
Table 14.2.5.2	Time to first Asthma CompEx event (days) based on the period from baseline to Week 24 - Cox-regression analysis	ITT population
Figure 14.2.5	Time to first Asthma CompEx event (days), Kaplan-Meier plot	ITT population
Table 14.2.5.3	Asthma CompEx event rate through Week 16, summary statistics	ITT population
Table 14.2.5.4	Asthma CompEx event rate through Week 24, summary statistics	ITT population
Table 14.2.5.5	Asthma CompEx event through Week 16, negative binomial model	ITT population
Table 14.2.5.6	Asthma CompEx event through Week 24, negative binomial model	ITT population
14.2 AO		
Table 14.2.6.1	Airwave oscillometry parameters by visit, summary statistics	ITT population
Table 14.2.6.2	Change from baseline through Week 16 in airwave oscillometry parameters treatment comparisons, MMRM	ITT population
Figure 14.2.6	Change from baseline through Week 16 in airwave oscillometry parameters, LSMeans (80% CI)	ITT population
14.2 Exacerbations		

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Table 14.2.7.1	Asthma exacerbations event rate through Week 16, summary statistics	ITT population
Figure 14.2.7.1	Time and duration of Asthma exacerbations	ITT population
Figure 14.2.7.2	Time to first Asthma exacerbation (days), Kaplan-Meier plot	ITT population
Table 14.2.7.2	Asthma exacerbations through Week 16, negative binomial model	ITT population
Table 14.2.7.3	Hospitalised asthma exacerbations through Week 16, negative binomial model	ITT population
Table 14.2.7.4	Time to first Asthma exacerbation (days) based on the period from baseline to Week 16 - Cox-regression analysis	ITT population
Table 14.2.7.5	Time to first Asthma exacerbation (days) based on the period from baseline to Week 24 - Cox-regression analysis	ITT population
14.2 Exploratory Diary + ePRO		
Table 14.2.8.1	2-weekly mean daily rescue medication usage (puffs/day) through Week 24, summary statistics	ITT population
Table 14.2.8.2	Change from baseline through Week 24 in 2-weekly mean daily rescue medication usage treatment comparisons, MMRM	ITT population
Figure 14.2.8	Change from baseline through Week 24 in 2-weekly mean daily rescue medication usage, LSMeans (80% CI)	ITT population
Table 14.2.9.1	2-weekly mean asthma symptom score through Week 24, summary statistics	ITT population

Table 14.2.9.2	Change from baseline through Week 24 in 2-weekly mean asthma symptom score treatment comparisons, MMRM	ITT population
Figure 14.2.9	Change from baseline through Week 24 in 2-weekly mean asthma symptom score, LSMeans (80% CI)	ITT population
Table 14.2.10.1	2-weekly mean number of night time awakenings through Week 24, summary statistics	ITT population
Table 14.2.10.2	Change from baseline through Week 24 in 2-weekly mean number of night time awakenings treatment comparisons, MMRM	ITT population
Figure 14.2.10	Change from baseline through Week 24 in 2-weekly mean number of night time awakenings, LSMeans (80% CI)	ITT population
Table 14.2.11	PGI-BR responses at Week 16	ITT population
14.2 Exploratory Biomarker Outcome		
Table 14.2.12.1	Plasma EDN by visit, summary statistics	ITT population
Table 14.2.12.2	Percent and relative change from baseline through Week 24 in plasma EDN treatment comparisons, MMRM	ITT population
Figure 14.2.12	Percent change from baseline through Week 24 in plasma EDN, LSMeans (80% CI)	ITT population
Table 14.2.13.1	Total IgE by visit, summary statistics	ITT population

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Table 14.2.13.2	Percent and relative change from baseline through Week 24 in total IgE treatment comparisons, MMRM	ITT population
Figure 14.2.13	Percent change from baseline through Week 24 in total IgE, LSMeans (80% CI) (ITT population)	ITT population
Table 14.2.14.1	sST2 by visit, summary statistics	ITT population
Table 14.2.14.2	Percent and relative change from baseline to Week 16 in sST2 treatment comparisons, ANCOVA	ITT population
14.2 Inflammatory airway biomarkers		
Table 14.2.15.1	Concentration of FeNO by visit, summary statistics	ITT population
Table 14.2.15.2	Percent and relative change from baseline to Week 16 in concentration of FeNO treatment comparisons, MMRM	ITT population
Figure 14.2.15	Percent change from baseline through Week 16 in concentration of FeNO, LSMeans (80% CI)	ITT population
Table 14.2.15.3	Percent and relative change from baseline through Week 24 in concentration of FeNO treatment comparisons, MMRM	ITT population
14.2 Nasal symptom control		
Table 14.2.16.1	SNOT-22 score by visit, summary statistics	ITT population

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Table 14.2.16.2	Change from baseline through Week 16 in SNOT-22 score treatment comparisons, MMRM	ITT population
Figure 14.2.16	Change from baseline through Week 16 in SNOT-22 score, LSMeans (80% CI)	ITT population
14.2 Exploratory cough sub-study		
Table 14.2.17.1	Objective cough measures over time, summary statistics	Exploratory cough sub-study population
Table 14.2.17.2	Percent and relative change from baseline to Week 16 in objective cough measures treatment comparisons, ANCOVA	Exploratory cough sub-study population
Table 14.2.18.1	Cough VAS by visit, summary statistics	Exploratory cough sub-study population
Table 14.2.18.2	Change from baseline to Week 16 in cough VAS treatment comparisons, ANCOVA	Exploratory cough sub-study population
PK Outputs		
Table 14.2.19.1	Summary of serum concentration (ug/L) of MEDI3506 by treatment	PK population
Table 14.2.19.2	Summary of serum concentrations (ug/L) of MEDI3506 over time by Anti-Drug Antibody category	PK population
Figure 14.2.19.1	Geometric mean (gSD) serum concentrations (ug/L) of MEDI3506 versus time by treatment (Linear scale)	PK population

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Figure 14.2.19.2	Individual serum concentrations (ug/L) of MEDI3506 versus time by treatment (Linear scale)	PK population
Figure 14.2.19.3	Individual serum concentrations (ug/L) time profile of MEDI3506 by Anti-Drug Antibody category - spaghetti plot	PK population
Immunogenicity		
Table 14.2.20.1	Summary of Anti-Drug Antibody responses during the study	As-treated population
Table 14.2.20.2	Anti-Drug Antibody results and titre summary by timepoint	As-treated population
Table 14.2.20.3	Pre-BD FEV1 (as measured in the clinic) at Week 16 by Anti-Drug Antibody category, summary statistics	As-treated population
Table 14.2.20.4	Pre-BD FEV1 (as measured in the clinic) at Week 24 by Anti-Drug Antibody category, summary statistics	As-treated population
Table 14.2.20.5	Adverse events during the treatment and follow-up periods in any category by Anti-Drug Antibody category	As-treated population
Table 14.2.20.6	Number of subjects with adverse events by system organ class and preferred term by Anti-Drug Antibody category	As-treated population
14.2 Exploratory PD Biomarker		
Table 14.2.21.1	Serum IL-5 by visit, summary statistics	ITT population

Table 14.2.21.2	Percent and relative change from baseline through Week 16 in serum IL-5 treatment comparisons, MMRM	ITT population
Figure 14.2.21.1	Percent change from baseline through Week 16 in serum IL-5, LSMeans (80% CI)	ITT population
Table 14.2.22.1	Serum IL13 by visit, summary statistics	ITT population
Table 14.2.22.2	Percent and relative change from baseline through Week 16 in serum IL13 treatment comparisons, MMRM	ITT population
Figure 14.2.22.1	Percent change from baseline through Week 16 in serum IL13, LSMeans (80% CI)	ITT population
Table 14.2.23.1	Serum IL33:ST2 by visit, summary statistics	ITT population
Table 14.2.23.2	Change from baseline through Week 16 in pre-BD FEV1(as measured in clinic) treatment comparisons by IL33:ST2 subgroups, MMRM	ITT population
Figure 14.2.23.1	Change from baseline through Week 16 in pre-BD FEV1 measured in the clinic, LSMeans (80% CI) by IL33:ST2 subgroups	ITT population
Table 14.2.24.1	Serum TSLP by visit, summary statistics	ITT population
Table 14.2.24.2	Percent and relative change from baseline through Week 16 in serum TSLP treatment comparisons, MMRM	ITT population

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Figure 14.2.24.1	Percent change from baseline through Week 16 in serum TSLP, LSMeans (80% CI)	ITT population
14.3 Safety evaluation data		
14.3.1 Exposure		
Table 14.3.1.1	Duration of exposure	As-treated population
Table 14.3.1.2	Treatment doses received and interruptions	As-treated population
14.3.2 All adverse events		
Table 14.3.2.1	Number of subjects with adverse events in any category	As-treated population
Table 14.3.2.2	Adverse events in any category - event counts	As-treated population
Table 14.3.2.3	Number of subjects with adverse events, most common (frequency of > 5%), by preferred term	As-treated population
Table 14.3.2.4	Number of subjects with adverse events by system organ class and preferred term	As-treated population
Table 14.3.2.5	Number of subjects with adverse events by preferred term and maximum reported toxicity grade	As-treated population
Figure 14.3.2	Adverse events, with a frequency of > 5% by preferred term and maximum reported toxicity grade	As-treated population
Table 14.3.2.6	Number of subjects with adverse events, by preferred term and relationship as assessed by investigator	As-treated population

Table 14.3.2.7	Number of adverse events, by system organ class and preferred term	As-treated population
Table 14.3.2.8	Number of subjects with adverse events, leading to dose interruption, by system organ class and preferred term	As-treated population
FDAAA1	Non-serious adverse events occurring in greater than 5% of subjects	As-treated population
14.3.3 Deaths		
Table 14.3.3.1	Number of subjects with adverse events with outcome of death by system organ class and preferred term	As-treated population
Table 14.3.3.2	Adverse events with outcome of death - key subject information	As-treated population
14.3.4 Serious AEs		
Table 14.3.4.1	Number of subjects with serious adverse events, by system organ class and preferred term	As-treated population
Table 14.3.4.2	Number of serious adverse events, by system organ class and preferred term	As-treated population
Table 14.3.4.3	Serious adverse events - key subject information	As-treated population
14.3.5 Discontinuation of investigational product due to AEs		
Table 14.3.5.1	Number of subjects with adverse events leading to discontinuation of investigational product, by system organ class and preferred term	As-treated population
Table 14.3.5.2	Adverse events leading to discontinuation of investigational product - key subject information	As-treated population

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14.3.6 Other significant AEs		
Table 14.3.6.1	Number of subjects with adverse events of special interest, by maximum reported toxicity grade	As-treated population
Table 14.3.6.2	Adverse events of special interest - list of preferred terms	As-treated population
Table 14.3.6.3	Number of subjects with injection site reaction, by maximum reported toxicity grade	As-treated population
Table 14.3.6.4	Number of subjects with COVID-19 related adverse events of special interest, by maximum reported toxicity grade	As-treated population
Table 14.3.6.5	Number of subjects with COVID-19 related serious adverse events of special interest, by maximum reported toxicity grade	As-treated population
14.3.7 Clinical laboratory evaluation		
Table 14.3.7.1.1	Haematology parameters over time	As-treated population
Table 14.3.7.1.2	Haematology parameters, baseline to maximum value during treatment	As-treated population
Table 14.3.7.1.3	Haematology parameters, baseline to minimum value during treatment	As-treated population
Table 14.3.7.2.1	Clinical chemistry parameters over time	As-treated population

Table 14.3.7.2.2	Clinical chemistry parameters, baseline to maximum value during treatment	As-treated population
Table 14.3.7.2.3	Clinical chemistry parameters, baseline to minimum value during treatment	As-treated population
Table 14.3.7.2.4	Subjects with potential Hy's Law - individual subject data	As-treated population
Figure 14.3.7.2.1	ALT versus total bilirubin, expressed as multiples of ULN	As-treated population
Figure 14.3.7.2.2	AST versus total bilirubin, expressed as multiples of ULN	As-treated population
Table 14.3.7.2.5	Maximum on-treatment ALT and AST by maximum total bilirubin for assessing Hy's Law criteria	As-treated population
Figure 14.3.7.2.3	Liver biochemistry test results over time - subjects with elevated ALT or AST, and elevated total bilirubin, at any point during the study following the start of study medication	As-treated population
Table 14.3.7.3.1	Urinalysis parameters over time	As-treated population
Table 14.3.7.3.2	Urinalysis parameters, baseline to maximum value during treatment	As-treated population

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Table 14.3.7.3.3	Urinalysis parameters, baseline versus maximum observation on treatment, shift table	As-treated population
14.3.8 Vital signs, ECG, physical findings and other observations		
14.3.8.1 Vital signs		
Table 14.3.8.1.1	Vital signs variables over time	As-treated population
Table 14.3.8.1.2	Vital signs, treatment-emergent changes outside predefined criteria - key subject information	As-treated population
14.3.8.2 ECG		
Table 14.3.8.2.1	ECG variables, over time	As-treated population
Table 14.3.8.2.2	ECG, baseline versus last observation on treatment	As-treated population
Table 14.3.8.2.3	ECG values outside predefined criteria - key subject information	As-treated population
Table 14.3.8.2.4	QTcF intervals, at any observation on treatment	As-treated population
14.3.8.x Other safety variables		
Table 14.3.8.3	Left ventricular ejection fraction (%), over time	As-treated population

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Table 14.3.8.4	NT-proBNP data over time	As-treated population
Table 14.3.8.5	NT-proBNP, baseline to maximum value during treatment	As-treated population
Table 14.3.8.6.1	Number of subjects tested positive for SARS-CoV-2 (by PCR or serology test) at end of study who were tested negative at baseline visit	As-treated population
Table 14.3.8.6.2	Summary of Treatment-emergent Adverse Events of Special Interest by COVID-19 result	As-treated population
14.3.8.7 Blood eosinophils		
Table 14.3.8.7.1	Blood eosinophils summary statistics	ITT population
Table 14.3.8.7.2	Percent and relative change from baseline through Week 24 in blood eosinophils treatment comparisons, MMRM	ITT population
Figure 14.3.8.7	Percent change from baseline through Week 24 in blood eosinophils, LSMeans (80% CI)	ITT population
Table 14.3.8.7.3	Blood eosinophils, baseline to maximum value during treatment	ITT population
16.1 Study information		
Appendix 16.1.6	Subjects receiving the various batches of investigational products	ITT population
Appendix 16.1.7	Randomisation scheme and codes	All randomised subjects

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16.2 Subject Data Listings		
Appendix 16.2.1.1	Discontinued subjects	ITT population
Appendix 16.2.1.2	Subjects completing the study	ITT population
Appendix 16.2.1.3	Subjects affected by the COVID-19 pandemic	ITT population
Appendix 16.2.2.1	Subjects with important protocol deviations	ITT population
Appendix 16.2.2.2	Subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic	ITT population
Appendix 16.2.3	Subjects excluded from any analysis set	
Appendix 16.2.4.1	Demographic and baseline characteristics	ITT population
Appendix 16.2.4.2	Asthma characteristics at baseline	ITT population
Appendix 16.2.4.3	Prior and concomitant medications	ITT population

Appendix 16.2.4.4	Prior and concomitant treatments containing ICS and combination of products containing ICS	ITT population
Appendix 16.2.5	Administration of investigational product	As-treated population
Appendix 16.2.6.1	Individual efficacy response data	ITT population
Appendix 16.2.6.2.1	Clinic spirometry	ITT population
Appendix 16.2.6.2.2	Home spirometry 2-weekly means	ITT population
Appendix 16.2.6.2.3	ACQ-6 questions and score	ITT population
Appendix 16.2.6.2.4	SGRQ questions, domains and total score	ITT population
Appendix 16.2.6.2.5	Compex events	ITT population
Appendix 16.2.6.2.6	FeNO results	ITT population
Appendix 16.2.6.2.7	Airway oscillometry parameters	ITT population

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Appendix 16.2.6.2.8	PGI-PR responses	ITT population
Appendix 16.2.6.2.9	SNOT-22 questions and score	ITT population
Appendix 16.2.6.2.10	Diary data, 2-weekly means	ITT population
Appendix 16.2.6.3	Objective cough measures	Exploratory cough sub-study population
Appendix 16.2.6.4	Drug concentration data	PK population
Appendix 16.2.6.5	Anti-Drug Antibody results	As-treated population
Appendix 16.2.6.6	Listing of ADA positive subjects, key subject information	As-treated population
Appendix 16.2.7.1	Adverse events	As-treated population
Appendix 16.2.7.2	Listing of adverse events among Anti-Drug Antibody positive subjects	As-treated population
Appendix 16.2.7.3	Adverse events for enrolled but not randomised subjects and for subjects who were not exposed to treatment	All subjects

Appendix 16.2.8.1	Individual laboratory measurement	As-treated population
Appendix 16.2.8.2	Other laboratory safety variables	As-treated population
Appendix 16.2.9	Individual vital signs data	As-treated population
Appendix 16.2.10.1	Electrocardiogram data	As-treated population
Appendix 16.2.10.2	Abnormalities in electrocardiogram	As-treated population
Appendix 16.2.10.3	Echocardiography data	As-treated population
Appendix 16.2.10.4	Abnormalities in echocardiography	As-treated population

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