Statistical Analysis Plan

Study Code	D5180C00013
Edition Number	3.0
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A Phase 2, Randomised, Double-blind, Parallel Group, Placebo Controlled Study to Evaluate the Effect of Tezepelumab on Airway Inflammation in Adults with Inadequately Controlled Asthma on Inhaled Corticosteroids and at least one additional asthma controller (CASCADE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AAER	Annualised asthma exacerbation rate
ACQ-6	Asthma control questionnaire-6
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse events of special interest
AHR	Airway hyper-responsiveness
ALT	Alanine aminotransferase
AO	Airwave oscillometry
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AX	Area under the reactance curve
BAL	Bronchoalveolar lavage
BD	Bronchodilator
BMI	Body mass index
BSA	Body surface area
BV5	Blood vessels less than $5mm^2$ in cross-sectional area
BV10	Blood vessels less than $10mm^2$ in cross-sectional area
CI	Confidence interval
CLCA1	Chloride channel accessory 1
COVID-19	Coronavirus Disease 2019
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse event
DBL	Database lock
DNA	Deoxyribonucleic acid
DRMI	Dropout reason-based multiple imputation
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDN	Eosinophil-derived neurotoxin

Abbreviation or special term	Explanation
EOT	End of treatment
ER	Emergency room
FAS	Full analysis set
$FEF_{25-75\%}$	Forced expiratory flow between 25% and 75% of the forced vital capacity
FEIA	Fluorescent enzyme immunoassay
FEV_1	Forced expiratory volume in 1 second
FFPE	Formalin fixed paraffin embedded
FRI	Functional respiratory imaging
FVC	Forced vital capacity
FeNO	Fractional exhaled nitric oxide
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IHC	Immunohistochemistry
IP	Investigational product
IPD	Investigational product discontinuation
ISH	In-situ hybridization
ITT	Intention-to-treat
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonists
LCM	Laser capture microdissection
LLOQ	Lower limit of quantification
LTRA	Leukotriene receptor antagonists
MACE	Major adverse cardiac events
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MI	Multiple imputation
nAb	Neutralizing antibodies
NC	Not calculable
NQ	Non-quantifiable
OCS	Oral corticosteroids
PD	Protocol deviation
PK	Pharmacokinetics

Abbreviation or special term	Explanation
POSTN	Periostin
PT	Preferred term
RT-qPCR	Quantitative reverse transcription polymerase chain reaction
Q4W	Every 4 weeks
QTc	Corrected QT interval
R5-R20	Peripheral airway resistance defined as the difference in resistance between 5 Hz (R5, total respiratory system resistance) and 20 Hz (R20, central resistance)
RBM	Reticular basement membrane
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SERPINB2	Serpin family B member 2
SoA	Schedule of activities
SOC	System organ class
T2	Type 2
TBL	Total bilirubin
UC	Urgent care
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
WHO	World health organisation

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
N/A	14-Dec-2018	Initially Approved SAP	Yes (V1.0)	
Study objectives	13-Nov-2020	Section 1.1.1, 1.1.2, 1.1.4: updated "Week 28" to "EOT"	Yes (V4.0)	Due to the possibility of additional visits and dosing during COVID-19 pandemic.
Study design	13-Nov-2020	Section 1.2: "During the COVID-19 pandemic, there is an option for patients to have an extra dose every 4 weeks up to 6 additional doses, as needed. For the last follow up visit, a phone call visit can replace an on-site visit" is added in the description of study design Figure 1, Study Design – Week 28 is now EOT and Week 40 is now EOS. Figure updated to align with implemented changes during COVID-19 (ie) extra dosing.	Yes (V4.0)	For consistency with the change on study design in amended protocol v4 due to the possibility of additional dosing during COVID-19 pandemic.
Analysis sets	05-Nov-2019	Sections 2.1.1, and 4.2: Evaluable analysis set has been added as the primary analysis set for efficacy analyses.	Yes (V3.0)	For consistency with protocol section 9.2.
Analysis sets	05-Nov-2019	Section 2.1.5: Main efficacy analyses use evaluable analysis set. Efficacy analyses using on-treatment data has been removed.	Yes (V3.0)	For consistency with protocol section 9.2. Efficacy analyses are conducted using evaluable analysis set and FAS.

Analysis sets	13-Nov-2020	Section 2.1.1: "and had an EOT visit date not greater than 8 weeks after date of last dose of IP" condition is added to definition of evaluable analysis set	Yes (V4.0)	Due to the possibility of additional dosings during COVID-19 pandemic.
General definitions	05-Nov-2019	Section 3.1.1: Baseline definition for spirometry variables has been updated.	Yes (V3.0)	The baseline has been updated to align with the collection of spirometry data and baseline value of interest.
Data presentations	05-Nov-2019	Section 3.1.1: Baseline definition for weekly mean scores derived from subject's paper diary has been removed.	Yes (V3.0)	The information captured by paper diary doesn't support the outcome analysis of weekly mean scores.
General definitions	05-Nov-2019	Section 3.1.3: Percent change from baseline has been added.	Yes (V3.0)	Details of calculation of percent change from baseline and handling of missing and zero are described.
Data presentations	05-Nov-2019	Section 3.1.7: Concomitant medications during post-treatment period has been updated.	Yes (V3.0)	Updated to include medications that started on or before last dose of IP + 35 days and either ended after date of last dose of IP + 35 days or is ongoing in the post-treatment period.
General definitions	05-Nov-2019	Section 3.1.8, 4.2.1, 4.2.4, and 4.2.5: Levels for stratification factor has been updated to < 150 cells/μL, 150 - < 300 cells/μL, ≥ 300 cells/μL.	Yes (V3.0)	For consistency with the randomisation process and also other tezepelumab studies.

General definitions	05-Nov-2019	Section 3.1.8: Subgroup by baseline blood eosinophils has been updated to be consistent with the cut-point for stratification factor.	Yes (V3.0)	For consistency with the randomisation process and also other tezepelumab studies.
General definitions	05-Nov-2019	Section 3.1.8: Subgroup by baseline body mass index and smoking status have been removed.	Yes (V3.0)	The subgroup analyses remained are the key subgroups of interest.
General definitions	05-Nov-2019	Sections 2.1.5, 3.1.7, and 3.3.2: The end date of on-treatment period for safety analyses has been updated to "date of last dose of IP + 35 days" from "date of last dose of IP + 33 days".	Yes (V3.0)	For consistency with protocol section 7.1.1.
General definitions	13-Nov-2020	Section 3.1.8: Add subgroups by baseline FeNO groups, baseline specific IgE status (FEIA), baseline perennial specific IgE status (FEIA), baseline seasonal specific IgE status (FEIA), baseline total serum IgE group, baseline interleukin-5 (IL-5) group, and baseline IL-13 group. Updated list of subgroup variables.	Yes (V4.0)	For consistency with other tezepelumab studies.
General definitions	13-Nov-2020	Section 4.2.4.1: Clarified the handling of zero in the calculation of ratio change and time point summary statistics using log-transformed data.	Yes	For calculation of summary statistics of ratio change using log-transformed data.
General definitions	13-Nov-2020	Section 4.2.7: Clarified the handling of zero for percent change.	Yes	For calculation of summary statistics of percent change when baseline value is zero.
General definitions	13-Nov-2020	Section 3.1.5: The planned treatment period is added and clarified efficacy data will be presented during planned treatment period, and safety data will be presented during on-study and/or on treatment period.	Yes (V4.0)	For consistency with other tezepelumab studies .

General definitions	13-Nov-2020	Section 3.1.5: updated “Week 28” to “EOT”	Yes (V4.0)	Due to the possibility of additional visits and dosing during COVID-19 pandemic.
General definitions	13-Nov-2020	Section 3.1.6: footnote is added to the visit window table to explain the impact of possibility of additional dosings during COVID-19 pandemic to the visit window calculation	Yes (V4.0)	Due to the possibility of additional visits and dosing during COVID-19 pandemic.
General definitions	13-Nov-2020	Section 3.1.7: removed the second and third conditions for concomitant medications during post-treatment period	Yes (V4.0)	For consistency with other tezepelumab studies .
Primary and secondary endpoints	05-Nov-2019	Section 3.2: updated “Week 28” to “EOT”.	Yes (V4.0)	Due to the possibility of additional visits and dosing during COVID-19 pandemic
Primary and secondary endpoints	05-Nov-2019	Section 4.2.4 and 4.2.5: Summary statistics and model for supportive variable of absolute change from baseline to week 28 in the primary and secondary efficacy endpoints have been added.	Yes (V3.0)	For consistency with protocol section 9.3.
Primary and secondary endpoints	05-Nov-2019	Section 4.2.4.3: Subgroup analysis has been updated.	Yes (V3.0)	Subgroup analyses and the model have been updated to reflect subgroups of interest and the covariates in the model.
Primary and secondary endpoints	05-Nov-2019	Section 4.2.6: Updated to “Any sensitivity analyses will be determined and documented prior to database lock of the study.”	NA	The sensitivity analysis will be determined prior to database lock of the study.
Primary and secondary endpoints	13-Nov-2020	Section 4.2.4.1: Clarified the primary variables T cells includes CD3+ and CD4+ variables, mast cells includes mast cells tryptase+ and mast cells chymase+ variables.	Yes	Clarification of primary endpoints

Primary and secondary endpoints	13-Nov-2020	Section 4.2.4.1: Clarified the formula of calculation of coefficient of variation of geometric mean.	Yes	For calculation of summary statistics using log-transformed data.
Primary and secondary endpoints	13-Nov-2020	Section 3.2, 4.1, 4.2.4, and 4.2.5: updated "Week 28" to "EOT"	Yes (V4.0)	Due to the possibility of additional visits and dosing during COVID-19 pandemic.
Primary and secondary endpoints	13-Nov-2020	Section 4.2.4.3: Added subgroups analyses by baseline blood eosinophils group, baseline FeNO groups, and baseline perennial specific IgE status (FEIA). Clarified that for model-based analyses, if any of the subgroups have fewer than 10 subjects in one or both treatment groups, this subgroup level will not be included in the model.	Yes (V4.0)	For consistency other tezepelumab studies .
Primary and secondary endpoints	13-Nov-2020	Section 4.2.5: Add subgroups of RBM thickness by baseline blood eosinophils group, baseline FeNO groups, and baseline specific IgE status (FEIA) using evaluable analysis set.	Yes (V4.0)	For consistency other tezepelumab studies .
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Pharmacokinetics and immunogenicity	05-Nov-2019	Section 1.1.4, 3.4, and 4.2.9.3: Neutralising antibodies (nAb) has been removed from immunogenicity endpoint.	Yes (V3.0)	For consistency with protocol section 9.3.4.8.

Pharmacokinetics and immunogenicity	13-Nov-2020	Section 4.2.9: Clarified PK analysis set, PK and ADA presented for on-study period, and timepoints and criteria of data for the by-visit summary. Clarified effect of ADA on PK and safety outcomes may be evaluated, if appropriate.	Yes (V4.0)	For consistency with other tezepelumab studies .
Data presentations	05-Nov-2019	Section 2.2: Important protocol deviations list has been updated.	Yes (V3.0)	For consistency with non-compliance handling plan (NHP).
Data presentations	05-Nov-2019	Section 3.1.1, 3.3.6 and 4.2.8.4: “12-lead ECG” has been updated to “12- or 15-lead ECG”	Yes (V3.0)	For consistency with protocol section 8.2.5.
Data presentations	05-Nov-2019	Section 3.3.7 and 4.2.8.5: Each component of physical examinations recorded as normal or abnormal and the summary data have been removed.	Yes (V3.0)	Data are not collected as described.
Data presentations	13-Nov-2020	Section 4.2.1: Demography, baseline data, medical and surgical history, stratification factor, and IPDs will be summarized using FAS. Demographic, subject characteristics at baseline, lung function at baseline, asthma characteristics at study entry, relevant disease related treatment at baseline will also be summarised by randomised treatment group using evaluable analysis set.	Yes (V4.0)	Demography and baseline data have been updated to align with the conduct of study and analyses of interest.
Data presentations	13-Nov-2020	Section 4.2.2: Allowed and disallowed medications during the prior, concomitant (on-treatment), and concomitant (post-treatment) will be presented for FAS.	Yes (V4.0)	For consistency with protocol section 9.2. to align with the conduct of study and analyses of interest.

Data presentations	4-Oct-2020	Section 4.2.2: Total daily OCS dose converted to a prednisone equivalent will be summarised. Conversion factors are added in Appendix 8.2.	Yes (V4.0)	For consistency with other tezepelumab studies.
Data presentations	05-Nov-2019	Section 4.2.3: The summary of compliance with the regularly scheduled ICS/LABA asthma inhaler as recorded in the daily diary has been removed.	NA	The information captured by paper diary doesn't support the summary.
Data presentations	13-Nov-2020	Section 4.2.4.1, 4.2.4.3: Analyses of absolute change from baseline to EOT will be presented based on evaluable analysis set. Subgroup analyses will be presented based on evaluable analysis set.	Yes (V4.0)	Clarification of analyses
Data presentations	13-Nov-2020	Section 4.2.5: Analyses of secondary efficacy variables will be presented based on evaluable analysis set.	Yes (V4.0)	Clarification of analyses
Data presentations	05-Nov-2019	Section 4.2.4, 4.2.5, and 4.2.7: Summary statistics have been updated to include geometric mean, coefficient of variation of geometric mean and SD of log.	Yes (V3.0)	Summary statistics have been updated to align with data presentation of interest.
Data presentations	13-Nov-2020	Section 4.2.4.1: Clarified summary statistics for absolute change from baseline to EOT will include number of subjects, mean, SD, median, minimum, and maximum based on evaluable analysis set.	Yes (V4.0)	Summary statistics have been updated to align with data presentation of interest.
Data presentations	13-Nov-2020	Section 4.2.4.1: Clarified primary endpoints will be presented in the unit cells per mm^2.	Yes	Summary statistics have been updated to align with data presentation of interest.

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Data presentations	05-Nov-2019	Section 4.2.8.1: AEs will be sorted by descending frequency order in the tezepelumab treatment group. Added exposure-adjusted summaries by SOC and PT for all AEs.	NA	Clarification of presentation in outputs
Data presentations	05-Nov-2019	Section 4.2.8.2: All laboratory data presented in SI units.	NA	For consistency with protocol section 9.3.5.3.
Data presentations	05-Nov-2019	Section 4.2.8.2: Shift table for urinalysis will display negative, positive, or strongly positive and missing values.	NA	For consistency with protocol section 9.3.5.3.
Data presentations	13-Nov-2020	Section 4.2.8.2, 4.2.8.3 and 4.2.8.4: Clarified missing category will be removed form shift tables.	Yes	Updated to align with the data of interest.
Data presentations	05-Nov-2019	Section 4.2.8.2, 4.2.8.3 and 4.2.8.4: The laboratory data, vital signs and ECG data are summarised for the on-study period.	Yes (V3.0)	Clarification of study period summarised
Data presentations	05-Nov-2019	Section 4.2.9.2: ELF-to-serum tezepelumab concentrations ratio has been added.	NA	Updated to align with the PK data of interest.
Data presentations	13-Nov-2020	Section 4.2.1: “or later due to COVID-19 pandemic” is added to clarify the possibility of longer time in the KM plots;	Yes (V4.0)	Due to the possibility of additional visits and dosing during COVID-19 pandemic.

		Clarified BMI groups definitions. Updated list of baseline characteristics variables to be presented.		For consistency with other tezepelumab studies .
Data presentations	13-Nov-2020	Section 4.2.2: “on or” is added to definition of maintenance medications	Yes	For consistency with other tezepelumab studies.
Data presentations	13-Nov-2020	Section 4.2.8.1: Clarified AE causality and maximum intensity will be summarised by PT; Section 4.2.8.1, Appendix 8.1: removed the broader definition of hypersensitivity, anaphylactic reaction and anaphylactoid shock conditions and related supporting analyses	Yes	For consistency with other tezepelumab studies.
COVID-19 related analyses	13-Nov-2020	Appendix 8.3: Add analyses to assess the impact of the COVID-19 pandemic, including violations and deviations, subject disposition, demography and baseline characteristics, exposure and compliance, primary efficacy analyses, and adverse events. Clarified the COVID-19 related sensitivity analysis for primary efficacy endpoints, ie, ratio change from baseline to Week 28 in the 6 airway submucosal inflammatory cells variables, will be performed including all subjects in the evaluable analysis set who had an EOT assessment at Week 28.	Yes (V4.0)	Added COVID-19 related analyses to describe the impact of COVID-19.
Other	05-Nov-2019	Section 6 (Change of analysis from protocol): Change in the stratification factor thresholds is documented. No changes have been made to the randomisation process	Yes	For consistency with the randomisation process and other tezepelumab studies
Other	13-Nov-2020	Section 6 (Change of analysis from protocol): Updated the analyses by T2 status.	Yes (V4.0)	T2 status related analyses will be based on RT-qPCR and

				serve as exploratory endpoints due to a serious breach.
Other	05-Nov-2019	Section 7 (References): Sampson et al 2006 is added.	NA	Inclusion of required reference

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5180C00013. The SAP describes the statistical analyses specified in the latest version of the clinical study protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

1.1 Study objectives

1.1.1 Primary objective

Primary Objective	Outcome Measures:
To explore the airway anti-inflammatory effect of tezepelumab	Outcome Variable: The change, expressed as a ratio, in number of airway submucosal inflammatory cells/mm^2 of bronchoscopic biopsies from baseline to end of treatment (EOT). Airway submucosal inflammatory cells will include eosinophils, neutrophils, T cells and mast cells. Outcome Measure: Ratio of tezepelumab to placebo at EOT

1.1.2 Secondary objectives

Secondary Objectives	Outcome Measures:
To explore the effect of tezepelumab on reticular basement membrane (RBM) thickening	Outcome Variable: The change, expressed as a ratio, in RBM thickness determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT Outcome Measure: Ratio of tezepelumab to placebo at EOT
To explore the effect of tezepelumab on airway epithelial integrity	Outcome Variable: The change, expressed as a ratio, in % airway epithelial integrity determined by microscopic evaluation of bronchoscopic biopsies from baseline to EOT Outcome Measure: Ratio of tezepelumab to placebo at EOT
To explore the airway anti-inflammatory effect of tezepelumab across the spectrum of Type 2 (T2) status by three gene mean derived from bronchial brushing ribonucleic acid (RNA) transcriptomics	Outcome Variable: The change, expressed as a ratio, in number of airway submucosal inflammatory cells per mm^2 determined by microscopic evaluation of bronchoscopic biopsies from baseline up to week 28 in subjects across the spectrum of T2 status Outcome Measure: Ratio of tezepelumab to placebo at week 28 across the spectrum of T2 status.

1.1.3 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of tezepelumab	Adverse events (AEs)/serious adverse events (SAEs)/adverse events of special interest (AESIs) Clinical chemistry/hematology/urinalysis Vital signs Electrocardiograms (ECGs)

1.1.4 Exploratory objectives

Exploratory Objectives:	Outcome Measures:
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The blood sample for DNA isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. The results

of the analyses will be reported separately from the clinical study report (CSR) in a scientific report or publication.

1.2 Study design

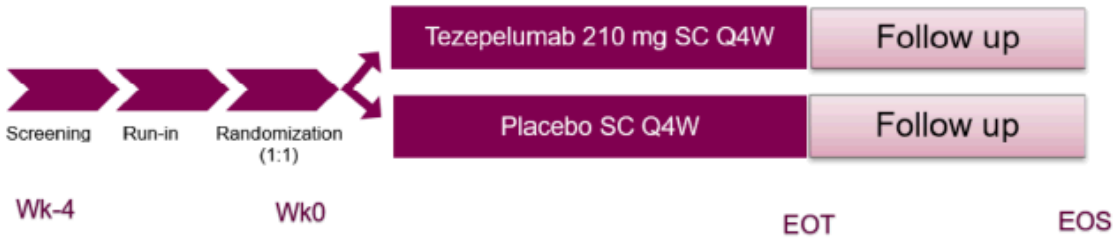
This is a phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the effect of tezepelumab on airway inflammation in approximately 110 adults with inadequately controlled moderate-to-severe asthma. Subjects will have background asthma therapy of medium- or high dose inhaled corticosteroids (ICS) plus at least one additional asthma controller medication, such as a long-acting β2-agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), cromone, and theophylline, with or without maintenance oral corticosteroids (OCS) from screening and throughout the study including the follow-up period.

The study will consist of a screening/run-in period of up to 4 weeks, a treatment period of 28 weeks and a post-treatment follow-up period of 12 weeks. One dose level of tezepelumab, 210 mg will be compared with placebo administered subcutaneously every 4 weeks (Q4W) over the treatment period. Subjects who discontinue investigational product (IP) during the study will be encouraged to undergo appropriate study visits/procedures for the full 40-week period. Any new treatments that are initiated will be recorded. Subjects who complete the 28-week study visit will complete a 12 week off-treatment follow-up period for assessment of safety parameters and ADAs. During the COVID-19 pandemic, there is an option for patients to have an extra dose every 4 weeks up to 6 additional doses, as needed. For the last follow up visit, a phone call and/or a virtual visit can replace an on-site visit.

The study aims to randomise subjects across the spectrum of T2 status. To ensure this, the study will randomise approximately 30% of subjects with < 150 blood eosinophils/µL, approximately 30% of subjects with 150 - < 300 blood eosinophils/µL and approximately 40% of subjects with ≥ 300 blood eosinophils/µL.

For an overview of the study design see Figure 1.

Figure 1 Study Design



1.3 Number of subjects

The study is sized to explore reductions in airway submucosal inflammation, from baseline to EOT for tezepelumab, versus placebo in the overall study population and across the T2 continuum.

The sample size chosen is based on the change from baseline to EOT in number of airway submucosal eosinophils and in number of airway submucosal neutrophils (ratio of tezepelumab to placebo).

It is estimated that 50 subjects in each treatment arm will provide (using a 2-sided test with a nominal 10% significance level for each endpoint):

- 80% power to observe a reduction in number of airway submucosal eosinophils if the true effect is a 2.7-fold difference versus placebo (assuming standard deviation on log scale of 1.87 and 2.06 for placebo and tezepelumab respectively based on tralokinumab study D2210C00014).

- >90% power to observe a reduction in number of airway submucosal neutrophils if the true effect is a 2.7-fold difference versus placebo (assuming standard deviation on log scale of 0.71 and 0.97 for placebo and tezepelumab respectively based on tralokinumab study D2210C00014).

This sample size allows exploratory assessment of the effect of tezepelumab on airway inflammation within quartiles across the T2 continuum and within other subgroups of interest. It is assumed that a small proportion of subjects will not have an evaluable primary endpoint value due to failed biopsies. To account for this and subject drop-outs, 55 subjects will be randomised in each treatment arm. A 2.7 fold change has been chosen because it is within the range of effect sizes observed with Nucala (Haldar et al 2009) and Fasenra (Laviolette et al 2013).

2. ANALYSIS SETS

2.1 Definition of analysis sets

All subjects analysis set:
This analysis set comprises all enrolled subjects who signed the informed consent form, and will be used for reporting of disposition including screen failures.

Randomised subjects analysis set:
This analysis set comprises all subjects randomised to study treatment, irrespective of whether IP was subsequently taken, and will also be used for reporting of disposition.

2.1.1 Efficacy analysis set

Full analysis set (FAS)

This analysis set comprises all subjects randomised to study treatment who received at least one dose of IP, irrespective of their protocol adherence and continued participation in the study.

Evaluable analysis set

This analysis set comprises all subjects randomised to study treatment who completed at least 20 weeks of study treatment and had an EOT visit date not greater than 8 weeks after date of last dose of IP.

Efficacy analyses will be performed using all subjects in the evaluable analysis set unless otherwise stated, with subjects classified by their randomized treatment according to the intention-to-treat (ITT) principle. Subjects will be analysed according to their randomised treatment (including in the case of any discrepancies between randomised and actual treatment).

The evaluable analysis set and FAS specifies which subjects are included in efficacy analyses. Details of which data are included in efficacy analyses for these subjects are given in the respective sections, notably in Section 3.1.5 and Section 4.2.

Certain types of exploratory efficacy data are planned to be captured in a subset of participating subjects who have given an additional consent to participate in such a sub-study. Where this is the case, the analysis will use the subset of subjects in the evaluable analysis set for which any data of the relevant type are available. No formal sub-study analysis sets will be explicitly defined for this purpose.

2.1.2 Safety analysis set

Safety analysis set

This analysis set comprises all subjects who received at least one dose of IP.

Safety analyses will be performed using all subjects in the safety analysis set. Subjects will be analysed according to their actual treatment in the case of any discrepancies between randomised and actual treatment. Specifically, a subject who has on one or more occasions actually received active (tezepelumab) treatment will be assigned to the tezepelumab group, regardless of the randomised treatment assignment. A subject who has on no occasion actually received any active (tezepelumab) treatment will be assigned to the placebo group, regardless of the randomised treatment assignment.

Safety data will also be listed separately and discussed in the CSR for any subject who received a treatment at one or more visits which was not the randomised treatment.

Summaries of ADA will also be based on the safety analysis set, using the same approach to handle treatment dispensing errors.

2.1.3 Other analysis set

PK analysis set

This analysis set comprises all subjects in the FAS who received active (tezepelumab) treatment and had at least one detectable tezepelumab serum concentration from a PK blood sample collected post first dose which are assumed not to be affected by factors such as protocol deviations.

Summaries of PK will be based on the PK analysis set.

2.1.4 Handling of other issues which may impact analysis sets

If it is found that any subject has been randomised on more than one occasion (contrary to the protocol) under different subject numbers, either at the same site or at different sites, then the first subject occurrence will be included in the relevant analysis sets defined above, and only

data associated with that first subject occurrence used in all analysis. Data associated with the second (and any subsequent) occurrences of the same subject will be listed and discussed in the CSR. All data associated with duplicate randomisations will be reviewed, and decisions regarding the analysis and reporting of these data will be documented, prior to unblinding.

The above analysis set definitions assume the integrity of data captured from all participating sites in the trial. If it is deemed necessary to exclude subjects from analysis sets due to suspected fraud/other serious non-compliance at a particular site, or to perform sensitivity analyses with subjects from such a site removed for the same reason, this will be documented in this SAP (amended if necessary) where this is possible prior to database lock (DBL). Otherwise, it will be fully described in the CSR. The SAP will not be updated for this after DBL.

2.2 Violations and deviations

Only important PDs will be listed and tabulated in the CSR, and only for randomised subjects (i.e. not screening failures). These are defined as PDs which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety or well-being. They may include (but not be limited to):

- Subjects who were randomised even though they did not meet all inclusion criteria or at least one exclusion criteria applied
- Subjects who met discontinuation criteria for study treatment but were not withdrawn from study treatment
- Subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who received the wrong treatment or an incorrect dose
- Subjects who received a restricted or prohibited concomitant treatment.

All important PDs will be identified and documented by the study team prior to unblinding of the trial. As far as possible, the occurrence of important PDs will be monitored (blinded) during the trial, with the emphasis on their future prevention.

Except for the PK analysis set, PDs including important PDs, will not be used to exclude any subject from any analysis set, nor to exclude any data from subjects included in an analysis set.

The study non-compliance handling plan outlines the management of important PDs, and includes the proposed categories of important PDs in this trial. Any PDs which are not defined as important (excluding COVID-19 related PDs) will not be reported or discussed in the CSR.

The COVID-19 related violation and deviations are described in Appendix 8.3.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Definition of baseline

In general, the last non-missing measurement on or prior to the date of randomisation will serve as the baseline measurement for efficacy variables. If there is no value on or prior to the date of randomisation, then the baseline value will not be imputed, and will be set to missing.

In general, the last non-missing measurement prior to the first dose of study treatment will serve as the baseline measurement for safety, pharmacokinetic and immunogenicity variables. If there is no value prior to first dose of study treatment, then the baseline value will not be imputed, and will be set to missing.

Where unscheduled/repeat assessments are relevant and exist for any subject at a particular visit specified below, they will also be considered in the baseline definitions, provided they remain on or prior to the date of randomisation (efficacy) or prior to the date of first dose of study treatment (safety).

For daily assessments which are made in both morning and evening, the whole day is defined by the assessments in the evening and the following morning. The daily assessment will be considered missing if either evening or following morning is missing. However, some analyses may consider morning and evening separately.

For safety variables (vital signs, weight/body mass index (BMI), haematology, clinical chemistry, urinalysis, 12- or 15-lead ECG), baseline will be defined as the latest non-missing assessment prior to first dose. If no time is recorded for an assessment, and the assessment takes place at Visit 3b, this will be assumed to be a pre-dose assessment.

3.1.2 Absolute change from baseline

Absolute change from baseline is defined as *(post-baseline value – baseline value)*.

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

Unless otherwise specified, “change from baseline” is assumed to be the absolute change from baseline.

3.1.3 Percent change from baseline

Percent change from baseline is defined as [*(post-baseline value – baseline value)/baseline value] x 100%.*

Unless otherwise specified, if either the post-baseline value or the baseline value is missing, then the percent change from baseline will also be missing.

For percent change from baseline, if the baseline value for a subject is zero, the baseline value will be replaced by half the smallest observed value among subjects with non-zero values, before calculating the percent change from baseline. If both baseline and post-baseline values for a subject are zero, the value for the percent change is defined to be 0.

3.1.4 Reversibility

Percentage reversibility is defined as follows, for pre-BD and post-BD measurements taken on the same date:

%Reversibility = [(post-BD FEV_1 – pre-BD FEV_1)/pre-BD FEV_1] x *100%*

The FEV_1 post-BD measurement in the reversibility derivation is the measurement after up to 4 SABA inhalations.

3.1.5 Study periods

The following study periods are defined for analysis purposes:

- Screening/run-in period: starting on the date of the first study procedure and ending one day prior to randomisation (for randomised subjects) or on the date of the last study procedure (for screening failures). If any subject is re-screened, the latest available screening will be used for this purpose.
- Planned treatment period: starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the date of the EOT visit or earlier study withdrawal date (for subjects not followed up until the EOT visit)
- On-treatment period: starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on minimum (date of last dose of IP + 35 days, date of death, date of study withdrawal).
- Post-treatment period/Follow-up period: starting one day after the end date of on-treatment period and ending on the study completion or withdrawal date.
- On-study (on-treatment and post-treatment) period: starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the study completion or withdrawal date.

Efficacy analyses will use data collected during the planned treatment period, except for lung function and some biomarker data that will use data collected at the protocol specified time points for the on-study period.

Safety analyses will be presented for data collected during the on-treatment period and on-study period.

3.1.6 Visit windows

All summaries and analyses, both efficacy and safety, which are presented by time point (e.g. “Week 28”) will use a visit window to classify the data record, which is derived from the assessment date relative to the reference start date. This approach allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing (notably the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

Nominal database visit numbers will not be used in any summary or analysis by visit.

For efficacy variables, the reference start date is the date of randomisation, and relative day is therefore defined as *(date of assessment – date of randomisation) + 1*.

For safety variables, the reference start date is the date of first dose of IP, and relative day is therefore defined as *(date of assessment – date of first dose of IP) + 1*.

Any data collected at unscheduled or repeat visits will be listed, and will be included in baseline definitions (see Section 3.1.1), and in any definitions of maximum value, minimum value or last value within the relevant study period.

Data collected at unscheduled or repeat visits will also be included in visit windows, and therefore may be included in summaries or analyses by visit, or used in any sensitivity analyses which involve imputation of data from subjects with non-missing values to subjects with missing values. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled or repeat assessment within the same visit window, the non-missing value at the unscheduled/repeat assessment will replace the missing value at the scheduled visit.

If a subject has more than one non-missing value within the same visit window, the following rules will apply:

- The non-missing value closest to the target day will be selected for analysis at that visit
- If two non-missing values are the same distance from the target day, the earlier of the two values will be selected for analysis at that visit
- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time will be selected for analysis at that visit.
- If two non-missing values are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit.
- If there are multiple ADA samples in the same visit window with both positive and negative results, the sample with a positive result and the highest titre value should be selected.

If a subject has no value within a particular visit window, then the subject will have a missing value at that visit in summaries and analyses.

The same visit window definitions below will be used regardless of whether the planned treatment, on-treatment, or on-study period is used for analysis (see Section 3.1.5). In practice, each data record in the planned treatment period will be identified, and then additional flags are created according to whether it is in the on-treatment or post-treatment, or on-study periods. These flags will be used to select all eligible records for subsequent visit windowing, according to whether the derived visits are to be used in a planned treatment, on-treatment, or on-study period analysis. It should be noted that, if treatment was discontinued within a particular visit

window, the rules above for handling multiple values within the same visit window could select a different record according to whether a planned treatment period analysis or an on-treatment period analysis is needed.

In planned treatment period analysis, any off-treatment assessments measured at a follow-up visit (scheduled 16 weeks after last IP administration) which occurred earlier than scheduled follow-up visits week 32, week 36, week 40, or later due to COVID-19 pandemic will be considered in earlier planned treatment period visit windows, where applicable.

The following table summarises the visit windows to be used. "Visit window 1" corresponds to the full (mostly 4-weekly) protocol scheduling and will be used for all variables by default, including those variables which are not captured according to the full protocol schedule, and for which only certain weeks displayed in "Visit window 1" therefore apply. An assessment will be made during blinded review of the extent to which values for variables which do not follow the complete protocol schedule are falling outside the windows for the relevant weeks using "Visit window 1". Following blinded review, a decision may be made to apply one of the alternative visit window rules displayed below to any such variables.

Table 1 Visit windows

Time point	Target day	Visit window 1	Visit window 2 (if needed)	Visit window 3 (if needed)	Visit window 4 (if needed)
Baseline (Week 0)	1	See Section 3.1.1 for baseline definitions			
Week 2	15				
Week 4	29	2-42			
Week 8	57	43-70			
Week 12	85	71-98	2-140		2-140
Week 16	113	99-126			
Week 20	141	127-154			
Week 24	169	155-182			
Week 28/EOT*	197/EOT*	183-210/EOT*	141-210/EOT*	2-210/EOT*	141-210/EOT*
Follow-up Week 32*	225				
Follow-up Week 36*	253				
Follow-up Week 40*	281	211-294	211-294		

* During the COVID-19 pandemic unscheduled visits may occur at week 28, 32, 36, 40, 44 or until 48 so that sites may perform EOT assessments 4 weeks after last dose of IP. After EOT visit, there will be post-treatment follow-up period of 12 weeks. Data from EOT visit will be summarised as "EOT" time point without visit window applied.

Finally, it should be noted that a visit window approach will not be used for data captured on a device daily by the subject, which will be aggregated for analysis at each relevant time point by using a weekly mean or similar approach. For this purpose, the definition of the weekly mean is provided in the relevant endpoint derivation sections of this SAP.

3.1.7 Prior and concomitant medication

Medications taken by any subject at any time during the study will be coded using the anatomical therapeutic chemical (ATC) classification system within the world health organisation (WHO) drug dictionary.

Medications will be categorised for analysis according to their onset and end dates as follows:

- Prior medications:
  - end date ≤ date of first dose of IP
- Concomitant medications during on-treatment period:
  - end date > date of first dose of IP and start date ≤ minimum (date of last dose of IP + 35 days, date of death, date of study withdrawal), or
  - end date ongoing and start date ≤ minimum (date of last dose of IP + 35 days, date of death, date of study withdrawal)
- Concomitant medications during post-treatment period (for subjects still being followed up then):
  - start date > date of last dose of IP + 35 days

Essentially the above says that:

- Prior and concomitant medications are mutually exclusive.
- Concomitant medications on-treatment and post-treatment are also mutually exclusive (here, the word "concomitant" means concomitant with study procedures, irrespective of whether IP was still being taken). Specifically, a concomitant medication which started on-treatment and ended post-treatment will only be considered on-treatment.

If the medication record has a completely missing start date, the subject will be assumed to have been on the medication on the date of the first study procedure. If the medication record has a partially missing onset date (month/year or year only) which is the same as that for the end of IP treatment, it will be assumed to have started on-treatment. If the medication record has a partially missing onset date (month/year or year only) which is the same as that for the start of IP treatment, it will be assumed to have started before treatment.

If the medication record has a completely missing end date, the subject will be assumed to have been on the medication on the date of study completion or withdrawal. If the medication record has a partially missing end date (month/year or year only) which is the same as that for start of IP treatment, it will be assumed to have ended on-treatment. If the medication record has a partially missing end date (month/year or year only) which is the same as that for end of IP treatment, it will be assumed to have ended post-treatment.

3.1.8 Definition of subgroups

The following subgroups are defined for the purposes of efficacy subgroup analysis (indicated with a *) and/or demographic and baseline summaries:

- * Stratification factor - screening blood eosinophils strata (Visit 1): < 150 cells/µL, 150 - < 300 cells/µL, ≥ 300 cells/µL
- * Baseline blood eosinophils group based on values at randomisation visit (Visit 3b): < 150 cells/µL, 150 - < 300 cells/µL, ≥ 300 cells/µL
- * Gender: Male, Female
- * Race: White, Black or African American, Asian, Other
- * Age category: adults (≥ 65 years), adults (18 - <65 years)
- * Baseline FeNO group: <25 ppb, ≥25 ppb
- Baseline (any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA
    - "Any FEIA positive" requires 1 or more specific IgE panels using fluorescent enzyme immunoassay (FEIA) to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 12 panels to be available.
    - "All FEIA negative" requires all 12 specific IgE panels to be negative. If there are fewer than 12 panels with data available and none of these is positive, then IgE status is considered "Unknown FEIA".
    - Positive is defined as a value >=0.35 kU/L
- * Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA
    - "Any perennial FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 8 panels to be available.
    - "All perennial FEIA negative" requires all 8 specific IgE panels to be negative. If there are fewer than 8 panels with data available and none of these is positive, then IgE status is considered "Unknown perennial FEIA".
    - Positive is defined as a value ≥0.35 kU/L. The 8 panels include: American Cockroach, Cat Dander, D. farina, D. pteronyssinus, Dog Dander, German Cockroach, Mould Mix, Oriental Cockroach.
- Baseline seasonal specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA

- "Any seasonal FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 4 panels to be available.
- "All seasonal FEIA negative" requires all 4 specific IgE panels to be negative. If there are fewer than 4 panels with data available and none of these is positive, then IgE status is considered "Unknown seasonal FEIA"
- Positive is defined as a value ≥0.35 kU/L. The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.

- * Baseline total serum IgE group: < median, ≥ median
- * Baseline interleukin-5 (IL-5) group: < median, ≥ median
- * Baseline IL-13 group: < median, ≥ median
- ICS dose at study entry: medium, high (as defined in CSP Appendix F)
- OCS at baseline: present, absent
  - OCS at baseline will be defined as OCS administered at baseline for disease under study
- Baseline body mass index (BMI): <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2Geographical region: North America [incl. Canada and USA], Western Europe [incl. Denmark, Germany, and UK]
- Reversibility in FEV1 %: <12%, ≥12%
  - Reversibility in FEV1 (%) is [post-bronchodilator FEV1 (L) - pre-bronchodilator FEV1 (L)] / pre-bronchodilator FEV1 (L) * 100%
- Asthma controller therapy: 1, >1
- Country

3.1.9 Disposition

The following definitions will be used for time to event variables in Kaplan-Meier disposition plots:

Time to last dose of IP

Time to last dose of IP will be defined as follows:

Time to last dose (days) = [Date of last dose of IP from eCRF – date of first dose of IP] + 1.

Date of last dose of IP will be the date of last dose taken from the "Discontinuation of Investigational Product" eCRF page for all subjects; those who prematurely discontinue IP as well as those who complete IP dosing as per protocol.

Time to premature study withdrawal

Time to premature study withdrawal will be defined as follows:

Time to premature study withdrawal (days) = [study withdrawal date from eCRF – date of randomisation] + 1.

Study withdrawal date will be the completion or discontinuation date from the "Disposition" eCRF page, where any subject status other than "Completed" has been entered.

Subjects who did not prematurely withdraw from study will be censored at the completion or discontinuation date from the "Disposition" eCRF page, where subject status of "Completed" has been entered.

3.2 Derivation of efficacy variables

3.2.1 Primary endpoints

3.2.1.1 Change from baseline to EOT in number of airway inflammatory cells per mm^2

Bronchial biopsies will be performed at baseline (Visit 3b) and EOT . The number of airway inflammatory cells per mm^2 will be determined by microscopic evaluation of bronchoscopic biopsies separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+.

The primary efficacy variables will be the change, expressed as a ratio, in number of airway inflammatory cells per mm^2 from baseline to EOT i.e. (EOT/baseline) for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+.. Each cell type will be analysed separately.

Absolute change from baseline to EOT in number of airway inflammatory cells per mm^2 for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ are considered as supportive variables to the corresponding primary variables.

3.2.2 Secondary endpoints

3.2.2.1 Change from baseline to EOT in RBM thickness

RBM thickness (μm) will be determined by microscopic evaluation of bronchoscopic biopsies at baseline (Visit 3b) and EOT .

The change, expressed as ratio, in RBM thickness from baseline to EOT i.e. (EOT/baseline), will be a secondary outcome variable.

Absolute change from baseline to EOT in RBM thickness is considered as a supportive variable.

3.2.2.2 Change from baseline to EOT in % airway epithelial integrity

The % airway epithelial integrity, including intact, damaged, and denuded epithelium %, will be determined by microscopic evaluation of bronchoscopic biopsies at baseline (Visit 3b) and EOT.

The change, expressed as a ratio, in % airway epithelial integrity from baseline to EOT i.e. (EOT/baseline), will be a secondary outcome variable.

3.2.2.3 Change from baseline to EOT in number of airway inflammatory cells per mm^2 across the spectrum of T2 status

Transcriptomic analysis will be performed on the RNA sample obtained from bronchial brushing at baseline (Visit 3b) and EOT (Visit 11). The three gene mean, derived from epithelial expression levels of periostin (POSTN), chloride channel accessory 1 (CLCA1), and serpin family B member 2 (SERPINB2), has been demonstrated as a surrogate marker of T2-driven inflammation in mild to moderate asthmatics. This epithelial gene expression signature will be used to retrospectively determine the degree of T2 status of each individual at randomisation (Visit 3b).

The change, expressed as a ratio, in number of airway inflammatory cells per mm^2 from baseline to EOT i.e. (EOT/baseline) across the spectrum of T2 status for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ were the secondary outcome variables. Each cell type would have been analysed separately.

Absolute change from baseline to EOT in number of airway inflammatory cells per mm^2 across the spectrum of T2 status for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ are considered as supportive variables.

3.2.3 Exploratory endpoints

CCI

- CCI

- CCI

The change, expressed as a ratio, from baseline to EOT i.e. (EOT/baseline), will also be CCI

- CCI

:

CCI

[redacted]

- CCI

[redacted]

3.3 Derivation of Safety variables

3.3.1 Exposure to IP and treatment compliance

Extent of exposure to IP is defined as the number of days between the date of first dose of IP and the date of last dose of IP inclusive plus the number of days allowance for the dosing interval specified in on-treatment period for safety variables in Section 3.1.5, i.e.:

Extent of exposure (days) = minimum (date of last dose of IP + 35 days; date of death; date of study withdrawal) – date of first dose of IP + 1

This calculation does not consider any gaps in exposure caused by the subject missing one or more intermediate scheduled 4-weekly doses. Such cases will be identified in the CSR if they occur, but will not explicitly be accounted for in any analysis.

The total subject-years exposure for a treatment group will be derived as the sum of the individual subject extents of exposure (days) for that treatment group and divided by 365.25.

Treatment compliance will be calculated as follows:

Treatment compliance (%) = (total number of actual dosing occasions/total number of expected dosing occasions) x *100%*

In order to allow for subjects who discontinue IP early in the compliance calculation, the number of expected dosing occasions will be calculated as the number of scheduled dosing visits up to and including the last available dosing visit for that subject.

3.3.2 AEs - general

AEs experienced by any subject at any time during the entire study will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be summarised for analysis according to their onset date into the following study periods:

- AEs occurring during screening/run-in period: date of Visit 1 ≤ AE onset date < date of first dose of IP

- AEs occurring during on-treatment period: date of first dose of IP ≤ AE onset date ≤ minimum (date of last dose of IP + 35 days, date of death, date of study withdrawal)

- AEs occurring during post-treatment period (for subjects still being followed up then): date of last dose of IP + 35 days < AE onset date ≤ study completion or withdrawal date

- AEs occurring during on-study period: date of first dose of IP ≤ AE onset date ≤ study completion or withdrawal date.

If the AE has a completely missing (and unresolvable) onset date, then the AE will be assumed to have occurred during the on-treatment period, unless the end date indicates unambiguously that the AE resolved before treatment started. If the AE has a partially missing (and unresolvable) onset date, then the AE will also be assumed to have occurred during the on-treatment period, unless either the end date indicates unambiguously that the AE resolved before treatment started, or the partial onset date is in the month/year prior to start of treatment.

Exposure adjusted incidence rates will be defined as the number of subjects reporting adverse events divided by extent of exposure for each subject, where exposure will be defined (irrespective of whether they have had the AE) as in 3.3.1 for extent of exposure for the on-treatment summaries.

Study adjusted incidence rates will be defined as the number of subjects reporting adverse events divided by duration of the on-study period for each subject as defined in Section 3.1.5.

The total time at risk (years) for a treatment group will be derived as the sum of the individual subject times at risk (days) for that treatment group and divided by 365.25.

For exposure-adjusted summaries of all AEs, the time at risk for each subject will be calculated using the first formula based on date of last dose of IP for all subjects, irrespective of whether they have had the AE.

In all exposure-adjusted summaries of AEs, multiple occurrences of the same event for a particular subject will not be counted as separate events. A subject will either be considered to have no events of the type being summarised, or one or more occurrences of that event.

3.3.3 Adverse events of special interest

The protocol specifies AESIs as those which merit special attention in this trial, and for which derivation details (for those derived from the eCRF), or a statement when the derivation needs to be referenced externally to the SAP (for those derived from MedDRA dictionary terms), are given in Appendix 8.1.

Similar considerations apply to any additional supporting analysis of AESIs, in which MedDRA dictionary based definitions are used.

3.3.4 Laboratory variables

Clinical chemistry, haematology and urinalysis will be performed by a central laboratory according to the schedule and the variable specifications described in the CSP. Urine samples will be analysed locally and sent for analysis at the central laboratory only if a positive dipstick result for any parameter is observed.

Changes from baseline in continuous laboratory variables will be calculated at relevant visits as specified in Section 3.1.1 and Section 3.1.2.

In all analysis of continuous laboratory variables, any value recorded only as below lower limit of quantification (LLOQ) will be set to LLOQ and included in the analysis. Any value recorded only as above upper limit of quantification (ULOQ) will be set to ULOQ and included in the analysis. Absolute values will be compared to the relevant normal reference range, as provided by the central laboratory, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables.

For the purposes of shift tables, baseline will be defined as specified in Section 3.1.1. Minimum, maximum and last values calculated across all visits in the relevant study period will use all available values including those from unscheduled and repeat visits, and irrespective of whether the values have been selected for use in summaries using visit windows (see Section 3.1.6).

Liver function tests for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin (TBL) will also be evaluated as multiples of the upper limit of the normal reference range (ULN). Subjects who meet any of the following criteria at any time during the study will be flagged:

- AST $\geq$ 3 x ULN
- ALT $\geq$ 3 x ULN
- TBL $\geq$ 2 x ULN

Other multiples of ULN will also be used in the display of liver function tests.

3.3.5 Vital signs

Changes from baseline in vital signs variables (pulse rate, systolic blood pressure (BP), diastolic BP, respiratory rate, body temperature, body weight, and BMI) will be calculated at relevant visits as specified in Section 3.1.1 and Section 3.1.2.

BMI is calculated as:

BMI = Weight (kg) / [Height (m)]^2.

Absolute values and changes from baseline (where applicable) will be compared to the relevant reference range tabulated below, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the reference ranges will be flagged.

Table 2 Vital signs reference ranges

Parameter	Standard units	Lower limit	Upper limit	Change from baseline criteria
Diastolic blood pressure (sitting)	mmHg	60	100	±15

Table 2 Vital signs reference ranges

Parameter	Standard units	Lower limit	Upper limit	Change from baseline criteria
Systolic blood pressure (sitting)	mmHg	90	160	±30
Pulse rate (sitting)	Beats/min	50	100	±20
Respiratory rate	Breaths/min	8	20	
Body temperature	Celsius	36.0	37.5	
Weight	kg	40	150	

3.3.6 Electrocardiogram

Either 12-lead or 15-lead ECG measurements will be recorded in accordance with the protocol, with the baseline visit being defined as V1.

The outcome of the overall evaluation (normal, abnormal or borderline) will be taken directly from the eCRF, as will the assignment of clinically significance.

3.3.7 Physical examination

Complete and brief physical examinations will be performed at time points according to the SoA in the CSP. Assessments will be dependent on whether the examination is complete or brief, as described in Section 8.2.3 of the CSP. For the brief physical examination, only information on whether the assessment was performed or not is to be recorded.

Only physical examination results judged as a new clinically meaningful finding or a clinically meaningful aggravation of an existing finding by the investigator will be captured, and these will be reported as AEs.

3.4 Derivation of pharmacokinetic and immunogenicity variables

Serum samples for determination of tezepelumab concentrations and the presence of anti-drug antibodies (ADAs) will be collected at baseline prior to first IP administration, at multiple time points and before any IP administration during the treatment period, and at the end of the follow-up period, according to the SoA in the CSP. BAL samples will also be collected for determination of tezepelumab concentration at specified time points according to the SoA in the CSP.

Serum samples will be used to determine tezepelumab concentrations, and to measure the presence of ADA, according to validated assays performed by a designated third-party vendor. Tezepelumab concentrations in BAL will be evaluated using a qualified assay and reported separately from the CSR. Urea concentrations in both serum and BAL will also be evaluated using qualified assays to correct for the dilution factor of the BAL samples. Details of the bioanalytical methods used will be described in a separate bioanalytical report.

For immunogenicity, tiered analysis will be performed to include screening, confirmatory, and titre of ADA assay components. Samples that are confirmed positive for ADAs will be archived for possible testing for the presence of neutralizing antibodies (nAb).

The third party vendor analysing the PK samples will be unblinded to the randomised treatment assignments of all subjects; no one from the study team will have access to the PK or ADA data until after the study has been unblinded. The assay for determination of tezepelumab concentrations in serum or BAL will only be performed using samples for subjects randomised to tezepelumab. Subjects who are randomised to placebo will not have their PK samples analysed by the vendor laboratory. The ADA and urea samples from all subjects, regardless of treatment assignment, will be analysed.

Due to the limited sampling schedule, only tezepelumab concentration data will be available (for the tezepelumab group only); no other PK parameters will be derived for any analysis within the scope of this SAP.

4. ANAYSIS METHODS

4.1 General Principles

4.1.1 Statistical hypotheses for efficacy variables

The primary efficacy objective will be evaluated through statistical testing of the within subject change, expressed as a ratio, from baseline to EOT in number of airway submucosal inflammatory cells separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+. Subjects will be analysed using the evaluable analysis set with subjects classified by their randomised treatment according to the ITT principle.

The null hypothesis test H_0 will be: The ratio (tezepelumab/placebo) of the change, expressed as a ratio, from baseline to EOT for each primary and secondary endpoint between tezepelumab and placebo equals 1 and will be tested versus. H_1: The ratio (tezepelumab/placebo) of the change, expressed as a ratio, from baseline to EOT for each primary and secondary endpoint between tezepelumab and placebo is not equal to 1, i.e.,

H_0: ratio (tezepelumab/placebo) = 1

H_1: ratio (tezepelumab/placebo) $\neq$ 1

4.1.2 Testing strategy to account for multiplicity considerations

The statistical testing of change from baseline to EOT for each of the primary variables will be performed separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+.

The testing of individual secondary efficacy variables will be considered as supportive.

Nominal p-values will be reported for primary and secondary variables i.e. no adjustment of multiplicity will be performed.

The descriptive statistics will be summarised for primary, secondary and exploratory efficacy endpoints, safety, pharmacokinetic and immunogenicity variables.

4.2 Analysis methods

4.2.1 Subject disposition, demography and baseline characteristics

Subject disposition will be summarised using the all subjects analysis set. The number of enrolled subjects will be summarised. The number and percentage of subjects within each treatment group will be presented by the following categories: randomised, not randomised (and reason), received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), discontinued treatment but completed study assessments, completed treatment and completed study, completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and withdrawn from study (including reason). Subject recruitment by country and centre will also be summarised.

Disposition will also be provided for the number and percentage of randomised subjects who consented separately to participate in the optional sub-studies (e.g. DNA sampling).

The number and percentage of subjects, who discontinued IP, but remained in the study will be presented by treatment group and option of follow up (Section 1.2).

Kaplan-Meier plots will be produced summarising separately the time (in days) to last dose of IP and premature withdrawal from the study by randomised treatment group using FAS. Subjects without the premature event will be censored as described in Section 3.1.9.

Demographic data such as age, gender, race, and ethnic group (Hispanic or Latino, Not Hispanic or Latino) will be summarised by randomized treatment group using FAS. The stratification factor i.e. blood eosinophils count (< 150 cells/µL, 150 - < 300 cells/µL, ≥ 300 cells/µL) recorded at screening will be summarised by randomised treatment using FAS. All subgroups as defined in Section 3.1.8 will be summarised by randomised treatment group using FAS.

Various baseline characteristics will also be summarised by randomized treatment using FAS. These include respiratory disease histories, weight, height, BMI, smoking status, history of allergy, FEV1 (pre- and post-BD) and FEV1 reversibility, FEV1 % predicted (pre and post-BD), FVC (pre and post-BD), $FEF_{25-75\%}$ (pre and post-BD), FEV1/FVC(pre and post-BD), asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, number of asthma exacerbations requiring hospitalisations in the previous 12 months, and ACQ-6. The medical and surgical histories will be summarised by randomized treatment using FAS.

Baseline biomarker variables FeNO, blood eosinophils, allergic status, total serum IgE, baseline cytokines IL-5, and IL-13 will also be summarised by randomized treatment using FAS.

Medical and surgical histories will be summarised by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA using FAS.

The demographic, subject characteristics at baseline, lung function at baseline, asthma characteristics at study entry, relevant disease related treatment at baseline will also be summarised by randomised treatment group using evaluable analysis set.

Important PDs will be summarised by randomised treatment using FAS.

The number and percentage of subjects in each of the analysis sets defined in Section 2.1 will be summarised.

4.2.2 Prior and concomitant medications

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented by randomised treatment using FAS. Separate tables will be presented for all medications received during each of the following periods as defined in Section 3.1.7: prior, concomitant (on-treatment), concomitant (post-treatment).

Tables for maintenance medications (started on or prior to and ongoing after the first day of IP) will be produced. The number of subjects using ICS medications and other maintenance asthma medications at visit 1 and baseline, and baseline total daily dose of ICS medications will be summarised using FAS. The number of subjects using ICS medications and other maintenance asthma medications at baseline will also be summarised using evaluable analysis set. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per subject from the first day of IP to EOT will also be summarised.

Summary statistics will be produced of total daily OCS dose converted to a prednisone equivalent (for subjects taking OCS at baseline). Conversion factors to be applied for this purpose are given in Appendix 8.2.

Disallowed medications will include medications defined as prohibited according to Section 6.5 of the CSP. Disallowed medications include prohibited and restricted drugs; restricted drugs are considered a disallowed medication depending on timing of use, or if there are changes in dose and regimen during the study as defined in the CSP. They will be defined following a physician review (prior to database lock) of the unique combinations of ATC code classifications and generic terms captured.

Separate tables will be presented for all allowed and disallowed medications received during each of the following periods as defined in Section 3.1.7: prior, concomitant (on-treatment), concomitant (post-treatment), respectively.

Medications will be classified using the latest version of the WHO Drug Dictionary.

Percentages will be calculated relative to the number of subjects in FAS.

Data from subjects who discontinued IP, regardless of level of follow up chosen will, where possible and relevant, be included in the appropriate medication summaries.

Potential prior biologics use will be summarised separately, similarly to above.

4.2.3 Exposure and compliance

Exposure and treatment compliance derivation details are defined in Section 3.3.1.

Extent of exposure to IP, compliance, and total number of dosing occasions will be summarised by treatment group, for the safety analysis set.

The date and time of IP administrations, and all missed doses will be listed using the safety analysis set.

4.2.4 Primary outcome variables

4.2.4.1 Primary analyses

The primary variables of within subject change from baseline to EOT, expressed as ratio i.e. (EOT/baseline) in numbers of each of the airway submucosal inflammatory cells will be analysed using evaluable analysis set and FAS separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ using an analysis of covariance (ANCOVA) including baseline value, treatment, and stratification factor (screening blood eosinophils count: < 150 cells/μL, 150 - < 300 cells/μL, ≥ 300 cells/μL at Visit 1) as covariates. The analyses will be performed by using log-transformed data and estimated geometric means and the ratio of geometric means with both 2-sided 90% and 95% confidence intervals (CIs), and p-values will be presented. The results will also be summarised graphically using a forest plot.

If the change from baseline for a subject, expressed as a ratio, is zero, the value will be replaced by half the smallest observed value among the subjects with non-zero values, before doing the logarithmic transformation. If the baseline value for a subject is zero, the baseline value will be replaced by half the smallest observed value among subjects with non-zero values, before calculating the change from baseline. If both baseline and a post-baseline value for a subject is zero, the corresponding value for the ratio is defined to be 1.

Available values at both baseline and EOT are required for a subject to be included in the analysis and it is unlikely that a subject with a missing baseline value will undergo a second biopsy.

All hypothesis testing will be reported using 2-sided tests with a nominal 10% significance level and 90% CIs. For publishing purposes, 95% CIs will also be reported. The direction of interest for each of the primary endpoints is that the ratio tezepelumab/placebo is lower than 1.

The supportive variables of within subject absolute change from baseline to EOT in numbers of each of the airway submucosal inflammatory cells will be analysed using evaluable analysis set separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+, using the same ANCOVA model described for the primary variables. The analyses will be performed and estimated means and difference estimates with 2-sided 90% and 95% confidence intervals, and p-values will be presented. The results will also be summarised graphically using a forest plot.

Summary statistics including number of subjects, mean, standard deviation (SD), median, minimum, maximum, geometric mean, and coefficient of variation of geometric mean for absolute values at each visit in number of airway submucosal inflammatory cells will be presented separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+, based on the evaluable analysis set by randomised treatment group. For change from baseline to EOT, expressed as a ratio, summary statistics including number of subjects, median, minimum, maximum, geometric mean, coefficient of variation of geometric mean, and SD of log values will be presented. Coefficient of variation of geometric mean is calculated as √(exp(std^2)-1)*100%, where std is the standard deviation of the log-transformed values. For absolute change from baseline to EOT, summary statistics including number of subjects, mean, SD, median, minimum, and maximum will be presented based on evaluable analysis set.

For time point summary statistics using log-transformed values in efficacy variables, if a baseline or post-baseline value for a subject is zero, the value will be replaced by half the smallest observed value among subjects with non zero values, before calculating the log-transformed value.

4.2.4.2 Multiplicity adjustment of primary outcome variables

Nominal p-values will be calculated for airway submucosal inflammatory cells separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ . No multiplicity adjustment of primary outcome variables will be performed.

4.2.4.3 Subgroup analysis of primary outcome variables

Efficacy for the primary variables will be evaluated within each subgroup using the evaluable analysis set.

The subgroup analysis of the primary variables by stratification factor (screening blood eosinophils count: < 150 cells/μL, 150 - < 300 cells/μL, ≥ 300 cells/μL) will use the same ANCOVA model described for the primary variable in Section 4.2.4.1, and also include the stratification factor by treatment interaction. The subgroup analysis of primary variables by other subgroup factors, ie, gender, race, age, baseline FeNO group, baseline perennial specific IgE status (FEIA): allergic and non-allergic, baseline total serum IgE group, baseline IL-5 group, and baseline IL-13 group, will be analysed separately using the same ANCOVA model as in Section 4.2.4.1 with the addition of elements in the ANCOVA model for subgroup factor, and interactions between subgroup and treatment. The analysis of primary variables by baseline blood eosinophils subgroups will not include stratification factor as an element in the ANCOVA model. The analyses will be performed using log-transformed data. The estimated geometric means and the ratio of geometric means with 2-sided 90% and 95% CIs and p-values will be presented for each subgroup. Results will be summarised graphically using a forest plot.

Descriptive summaries of the primary variables will be presented for the specified categorical variables above, irrespective of how few subjects there are in any particular subgroups.

For model-based analyses, if any of the subgroups have fewer than 10 subjects in one or both treatment groups, this subgroup level will not be included in the model. If that leaves only one subgroup level, the model will not be fitted for that categorical variable. If it leaves more than one subgroup level, the model will be fitted using the remaining subgroups which have 10 or more subjects in both treatment groups.

The same summary statistics provided for the primary variables will be presented for each of the primary variables within all subgroups based on the evaluable analysis set by randomised treatment group.

4.2.5 Secondary outcome variables

The secondary variables of within subject change, expressed as a ratio, from baseline to EOT in RBM thickness and % airway epithelial integrity, will be analysed using evaluable analysis set and the same ANCOVA model described for the primary variable, which includes baseline value, treatment, and stratification factor as covariates. The analysis will also be performed by using log-transformed data and estimated geometric means and the ratio of geometric means

with 2-sided 90% and 95% confidence intervals, and p-values will be presented. The results will also be summarised graphically using a forest plot.

The secondary variables of within subject change, expressed as a ratio, from baseline to week 28 in numbers of each of the airway submucosal inflammatory cells for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ across the spectrum of T2 status, will be analyzed separately using the same ANCOVA model described for the primary variables with the addition of elements in the ANCOVA model for T2 quartile (categorical) and interactions between T2 quartile and treatment. The analyses will be performed by using log-transformed data. The ratio of geometric mean sand the ratio of geometric means with 2-sided 90% and 95% CIs, and p-values will be presented.

The supportive variables of within subject absolute change from baseline to week 28 in RBM thickness, % airway epithelial integrity, and numbers of each of the airway submucosal inflammatory cells for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+, and mast cells chymase+ across the spectrum of T2 status will be analysed separately using the same ANCOVA model described for the primary variables. The analyses will be performed and estimated means and difference estimates with 2-sided 90% and 95% confidence intervals, and p-values will be presented. The results will also be summarised graphically using a forest plot.

The subgroup analysis of RBM thickness by baseline blood eosinophils (< 150 cells/μL, 150 - < 300 cells/μL, ≥ 300 cells/μL), baseline FeNO group, and baseline perennial specific IgE status based on evaluable analysis set will be performed in the same manner as the subgroup analyses of primary variables.

The same summary statistics provided for the primary variables will be presented for each of the secondary and supportive variables and subgroup analyses of RBM thickness based on the evaluable analysis set by randomised treatment group.

To explore the relationship of change from baseline in primary variables and T2 status, the LOESS scatterplots will be generated for log-ratios i.e. (EOT/baseline) in inflammatory cell counts versus T2 status (continuous) by treatment group for each inflammatory cell type for evaluable analysis set. The box plots for log-ratios i.e. (EOT/baseline) in inflammatory cell counts will also be generated by treatment within each T2 quartile (categorical). The results of the T2 status analyses will be reported separately from the CSR in a scientific report or publication.

4.2.6 Sensitivity analyses for primary and secondary outcome variables

Any sensitivity analyses will be determined and documented prior to database lock of the study. The COVID-19 related sensitivity analyses for primary and secondary outcome variables are described in Appendix 8.3.

4.2.7 Exploratory objectives

CCI

CCI

[redacted]

CCI

[redacted]

4.2.8 Safety and tolerability

All safety variables will be summarised using the safety analysis set (see Section 2.1.2 for details).

4.2.8.1 AEs

AEs will be summarised separately for the on-treatment and on-study periods, as defined in Section 3.3.3 unless stated otherwise. All AE summaries will be presented by actual treatment group. AEs occurring during the screening/run-in period, or occurring post-treatment will be listed, but not summarised separately.

An overall summary table will be produced showing the number and percentage of subjects with at least one AE in each of the following categories: any AEs, SAEs, AEs with a fatal outcome, AEs leading to discontinuation of IP (DAEs), and AESIs. The total number of AEs in the different AE categories will also be presented as well as the number of subjects (i.e. accounting for multiple occurrences of the same event in a subject).

All AEs will be summarised by SOC and PT assigned to the event using the MedDRA dictionary by descending frequency order in the tezepelumab treatment group. For each PT, the

number and percentage of subjects reporting at least one occurrence of the event will be presented (i.e. subjects with multiple occurrences of the same PT will only be counted once).

Similar summaries by SOC and PT will also be presented for:

- SAEs
- Fatal AEs
- DAEs
- DAEs causally related to IP
- SAEs leading to discontinuation of IP
- Each AESI category separately
- The most common AEs (defined as those occurring in >3% of subjects in either treatment group) – by PT only

All AEs (by PT) will be summarised additionally by causality and maximum intensity. If a subject reports multiple occurrences within each PT, the maximum intensity will be taken as the highest recorded (the order being mild, moderate and severe) respectively.

Exposure-adjusted summaries by SOC and PT will also be presented for all AEs.

The COVID-19 related safety analyses are described in Appendix 8.3.

4.2.8.2 Laboratory data

All laboratory data will be presented in SI units. All continuous laboratory variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. These summaries will be produced for the on-study period, as defined in Section 3.1.5. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

Central laboratory normal reference ranges will be used for the identification of individual clinically important abnormalities. A shift table will be produced for each laboratory variable to display low, normal, and high values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual subject's laboratory value at baseline and at maximum/minimum/last value post-baseline will be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced. The diagonal line of no change will also be displayed on the shift plots.

Both shift tables and shift plots will be produced using all data for the on-study period, as defined in Section 3.1.5.

The frequencies of clinically noteworthy values (using normal reference ranges) occurring during the study will also be given.

In order to identify potential Hy's Law cases, maximum post-baseline TBL will be plotted separately against both maximum post-baseline ALT and AST, expressed as multiples of ULN. These plots will be produced on a log scale, with reference lines included at 2xULN for TBL, and at 3xULN for both ALT and AST. These plots will be produced using all data for the on-study period.

For all subjects who meet the biochemical criteria for Hy's Law (potential Hy's Law cases), the relevant laboratory variables may be tabulated showing all visits for these subjects.

Subjects with elevated ALT or AST in addition to elevated TBL at any time may be explored further graphically using individual subject profile plots.

For urinalysis data, a shift table will be generated for each variable to display negative (0), positive (trace or +) or strongly positive (++, +++, or >+++). The shift tables will present changes from baseline to maximum/last value post-baseline for each variable. All data for the on-study period will be used.

4.2.8.3 Vital signs

All vital signs variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. This will also include weight and BMI. These summaries will be produced for the on-study period, as defined in Section 3.1.5. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

AZ-defined reference ranges (see Section 3.3.5) will be used for the identification of individual abnormalities. A shift table will be produced for each vital signs variable to display low, normal, and high values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual subject's vital signs value at baseline and at maximum/minimum/last value post-baseline will be produced for each continuous vital signs variable.

Both shift tables and shift plots will be produced using all data for the on-study period, as defined in Section 3.1.5.

Subjects who have treatment-emergent changes from baseline outside the pre-defined AZ clinically important change criteria in Section 3.3.5 will be summarised. All data for the on-study period will be used.

4.2.8.4 12-lead or 15-lead ECG

A shift table will be produced for each ECG parameter to display normal (includes borderline), abnormal - not clinically significant, abnormal - clinically significant, and not done. The shift tables will present baseline and last observation post-baseline value for the on-study period, as defined in Section 3.1.5.

4.2.8.5 Physical examination

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE in AE reporting.

4.2.9 Pharmacokinetics and immunogenicity

4.2.9.1 Analysis of pharmacokinetics

All analyses of PK variables will be based on the PK analysis set as defined in Section 2.1.3.

Serum tezepelumab concentrations will be summarised at the protocol specified time points for the on-study-period using descriptive statistics (for the tezepelumab group only).

Serum samples for PK are scheduled to be collected at weeks 0, 12, EOT visit (or the premature IP discontinuation visit, where appropriate), and final follow-up at 12 weeks after EOT visit. Data will be assigned to weeks based on the windows defined in Section 3.1.6.

The following criteria will also apply for data to be included in the summary table:

- Only pre-dose samples at week 0.
- Only pre-dose samples at trough time points (week 12) that was also between ≥ 21 and ≤ 35 days post the previous dose.
- Only samples at EOT visit/premature IP discontinuation visit that were taken between ≥ 21 and ≤ 35 days post the last dose.
- Only samples at final follow-up visit that were taken between ≥ 98 and ≤ 126 days post the last dose.

For descriptive statistics of tezepelumab concentrations:

- If, at a given time point, 50% or less of the concentrations are non-quantifiable (NQ), the geometric mean, coefficient of variation (CV), arithmetic mean and SD will be calculated by substituting the lower limit of quantification (LLOQ) divided by 2 for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, arithmetic mean and SD will be reported as not calculable (NC)
- If all the concentrations are NQ, the geometric mean and arithmetic mean will be reported as NQ and the CV and SD as NC
- The median, minimum and maximum will also be reported.

The LLOQ of tezepelumab in serum will be 0.010 µg/mL.

The PK data may be merged with those from other clinical studies for a population-based meta-analysis. If performed, results of the meta-analysis will be presented in a separate pharmacometrics report outside of the CSR, and this is not considered further in this SAP.

4.2.9.2 Analysis of drug concentrations in BAL

BAL tezepelumab concentrations will be summarised at the protocol specified time points using descriptive statistics (for the tezepelumab group only)) separately from the CSR. For descriptive statistics of tezepelumab concentrations in BAL, the rules to handle non-

quantifiable concentrations will be the same as that for the serum tezepelumab PK data. The LLOQ of tezepelumab in BAL is TBD.

If appropriate, the tezepelumab concentrations in the epithelial lining fluid ($C_{teze,ELF}$) will be estimated based on the tezepelumab concentrations in BAL ($C_{teze,BAL}$) and the dilution factor (DF) derived based on the urea concentrations in serum ($C_{urea,serum}$) and BAL ($C_{urea,BAL}$) using the following equations:

$$DF = \frac{C_{urea,serum}}{C_{urea,BAL}}$$

$$C_{teze,ELF} = C_{teze,BAL} \times DF$$

If calculated, the ELF tezepelumab concentrations and ELF-to-serum tezepelumab concentrations ratio will be summarised at the protocol specified time points (week 0 and EOT visit) using descriptive statistics (for the tezepelumab group only). For descriptive statistics of tezepelumab concentrations in ELF and ELF-to-serum tezepelumab concentrations ratio, the rules to handle non-quantifiable concentrations will be the same as that for the serum tezepelumab PK data.

The results of this analysis will be reported separately from the CSR.

4.2.9.3 Analysis of immunogenicity

All analyses of immunogenicity variables will be based on the safety analysis set as defined in Section 2.1.3.

The number and percentages of ADA-positive subjects at each visit will be summarised by treatment group for the on-study period. Descriptive statistics including number of subjects, mean, SD, 1st quartile, median, 3rd quartile, and range of the actual ADA titres by treatment group and visit, where possible, will be provided.

The ADA status across the study for each subject will also be classified and summarised by treatment group. Specifically, the following ADA results will be evaluated as number and proportion of subjects in cohorts together with corresponding titre summaries. However, if the number of ADA positive subjects in the safety analysis set is small then the ADA variables may be listed only in the CSR:

- Subjects who are ADA positive at baseline and/or post-baseline (ADA prevalence).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and positive in at least one post baseline measurement.
- Subjects who are ADA positive at baseline regardless of post-baseline result.
- Subjects who are ADA positive post-baseline.
- Subjects who are ADA positive post-baseline and ADA negative at baseline (treatment induced ADA positive).

- Subjects who are ADA persistently positive; persistently positive is defined as 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.

- Subjects who are ADA transiently positive; transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.

- Subjects who are treatment boosted ADA positive, defined as baseline positive ADA titre that was boosted to a 4-fold or higher level following IP administration

- Subjects who are treatment emergent ADA (TE-ADA) positive (ADA incidence): defined as either treatment induced ADA positive or treatment boosted ADA positive.

For the overall ADA summary (i.e. calculation of the various ADA categories), all available ADA samples should be included in the analysis.

For ADA summaries at a single time point (e.g. baseline ADA or by visit) the corresponding titre summary will be based on the titre of the positive sample with the highest titre value for that particular visit.

For summaries across visits (e.g. ADA positive at any visit) the corresponding titre summaries will be based on the maximum titre of all positive samples for each subject.

The effect of ADA on PK and safety outcomes may be evaluated, if appropriate.

5. INTERIM ANALYSES

No interim analyses are planned in this trial.

An independent Data and Safety Monitoring Board (DSMB) will safeguard the interests of subjects by assessing the safety of the intervention. The DSMB will review safety data on a regular basis as set out in a DSMB charter. The data for review will be outlined in a DSMB charter. The DSMB will have access to individual treatment codes and will be able to merge these with the collected study data whilst the study is ongoing.

The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DSMB.

6. CHANGE OF ANALYSIS FROM PROTOCOL

The analyses proposed using T2 status determined by RNA transcriptomics of bronchial brushings at baseline may now be performed using T2 status determined by three gene mean derived from RT-qPCR from LCM excised epithelium from FFPE biopsy tissue at baseline due to laboratory error resulting in data loss, reported as a serious breach. Analyses relating to the T2 status, ie, change from baseline to EOT in number of airway inflammatory cells per mm^2 across the spectrum of T2 status derived from RT-qPCR, will be exploratory endpoint in this study, pending technical feasibility, and will be reported separately from the CSR.

7. REFERENCES

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8. APPENDIX

8.1 Adverse events of special interest

8.1.1 Anaphylactic reactions

Potential anaphylactic reactions will be defined on the basis of Sampson's criteria (see Sampson et al., 2006). These will be identified using a modified Standardized MedDRA Query (SMQ), with additional constraints on the timing of the AE onset date relative to the timing of the injection.

Confirmed anaphylactic reactions will be those defined following medical review of the preferred terms identified as potential anaphylactic reactions, as well as any relevant supporting data.

Immune complex disease will be defined using the PT defining immune complex disease (depending on current MedDRA version).

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to unblinding of the trial, and provided together with the study datasets at the time of submission.

8.1.2 Malignancy

Malignancy will be defined on the basis of an SMQ.

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to unblinding of the trial, and provided together with the study datasets at the time of submission.

8.1.3 Helminth infections

Helminth infection will use an investigator-driven definition, i.e. will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term where the dedicated Helminth Infection eCRF page was also completed for that event (linked by AE number), with AE onset date during the relevant study period for analysis.

8.1.4 Severe infections (as defined in the protocol)

Severe infections will use an investigator-driven definition, i.e. will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term with AE onset date during the relevant study period for analysis, which satisfies the following:

- "AE Category" on Adverse Events eCRF page marked as "Severe Infection", and one or more of the following:

- AE is serious ("Serious" on Adverse Events eCRF page marked as "Yes"), or
- AE required treatment with antiviral medications, intravenous antibiotics or medications for Helminth parasitic infection, or
- AE resulted in permanent discontinuation of study drug ("Action taken, investigational product" on Adverse Events eCRF page marked as "Drug permanently discontinued").

8.1.5 Injection site reactions

Injection site reactions will use an investigator-driven definition, i.e. will be directly determined from what is entered on the eCRF.

A subject will be considered to have this AESI if the subject has at least one preferred term with AE onset date during the relevant study period for analysis, which has "AE category" on the Adverse Events eCRF page marked as "Injection Site Reaction".

8.1.6 Opportunistic infections

Opportunistic infections will be defined using a pre-specified list of preferred terms (AZ defined SMQ).

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to unblinding of the trial, and provided together with the study datasets at the time of submission.

8.1.7 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to unblinding of the trial, and provided together with the study datasets at the time of submission.

8.2 OCS conversion factors for prednisone equivalents

Total daily OCS dose will be converted to a prednisone equivalent using the following table:

Table 3 Estimated OCS dose therapy equivalence

Oral Corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg

Oral Corticosteroid	Approximate equivalence dose
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg

For example, to convert a cortisone total daily dose to a prednisone equivalent total daily dose, a multiplication factor of 0.2 = 10/50 should be used.

8.3 Additional reporting to assess the impact of the COVID-19 pandemic

In order to assess the impact of the COVID-19 pandemic on the planned analyses, further additional summaries and analyses will be conducted. These are described below, with the section of the main SAP in which they relate to. The start date of the COVID-19 pandemic is defined as 11th March 2020; the date the World Health Organisation (WHO) declared it a pandemic. Where applicable, as described below, data will be presented prior to the start of the pandemic, and during the pandemic. No post-pandemic period is defined as it is expected that the majority of subjects will have completed the study before the end date of the pandemic can be defined.

Section 2.2 Violations and Deviations

All COVID-19 related IPDs will be grouped as described in Section 2.2 and summarised together with all non-COVID-19 related IPDs as described in Section 4.2.1. A listing of all COVID-19 related protocol deviations (important and non-important PDs) will be provided.

An additional summary will be provided of IPDs related to COVID-19, and IPDs excluding COVID-19 related IPDs separately by treatment group for the FAS.

Section 4.2.1 Subject disposition, demography and baseline characteristics

The number of subjects randomised prior to the COVID-19 pandemic, and number of subjects ongoing in the study, as well as ongoing in the planned treatment period during the COVID-19 pandemic will be summarised by treatment group for the FAS. The total duration of follow-up for subjects during the study will be summarised, together with the duration of follow-up during the COVID-19 pandemic, for the FAS. The proportion of time on study during the pandemic will also be provided by treatment group.

The number and percentage of subjects with at least one missed scheduled visit or changed format of scheduled visit will be summarised by treatment group for the FAS. Changed format of scheduled visit will be grouped into “On-site, partial visit”, “Remote visit”, “Other”. The number of subjects discontinuing IP or withdrawing from the study due to COVID-19 will also be summarised by treatment group.

A listing of all subjects impacted by COVID-19 will be produced with details of changed or missed visits and change of location of IP administration or missed IP administration.

Section 4.2.3 Exposure and Compliance

The number of subjects with missed IP doses due to COVID-19, including consecutive missed doses, will be summarised by treatment group. In addition, the number of IP doses administered by location (home, other) will be summarised by treatment group, for the safety analysis set.

Section 4.2.4.1 Primary outcome variables - primary analysis

To investigate any difference in treatment effect due to any additional IP doses administered to subjects at unscheduled weeks 28, 32, 36, 40, 44 and 48 during the COVID-19 pandemic outbreak, additional sensitivity analysis will be performed including only subjects in the evaluable analysis set who had an EOT assessment at Week 28. Analyses of the primary endpoints of within subject change, expressed as a ratio, from baseline to Week 28 in airway submucosal inflammatory cells will be performed separately for eosinophils, neutrophils, T cells (CD3+, and CD4+), mast cells tryptase+ and mast cells chymase+, using the same ANCOVA model described for the primary variables in Section 4.2.1. Results will also be included in the forest plot for the primary. Descriptive statistics will also be presented.

Section 4.2.8.1 Adverse Events

The number and percentage of subjects reporting COVID-19 AEs (as defined based on the COVID-19 MedDRA terms) will be summarised by system organ class (SOC) and preferred term (PT) for the on-treatment and on-study periods.

In addition, if there are more than 10 subjects reporting COVID-19 AEs, then the AE listing will be repeated including only these subjects, with details of all AEs reported by these subjects

A listing of subjects tested for COVID-19 and including test result will be provided.

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