
STATISTICAL ANALYSIS PLAN

Study Code D5180C00024

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**A Randomised, Double-Blind, Parallel-Group, Placebo-
Controlled 28-week Phase 3 Efficacy and Safety Study of
Tezepelumab in Reducing Oral Corticosteroid Use in Adults
with Oral Corticosteroid Dependent Asthma (SUNRISE)**

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AAER	Annualised asthma exacerbation rate
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AI	Adrenal Insufficiency
ALP	Alkaline phosphate
ALT	Alanine aminotransferase/transaminase
ANCOVA	Analysis of covariance
AQLQ(s)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
ASD	Asthma Symptom Diary
AST	Aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BD	Bronchodilator
BMI	Body mass index
BP	Blood pressure
COVID-19	Corona Virus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Adverse Event Leading to Discontinuation of Investigational Product
DBL	Database Lock
DNA	Deoxyribonucleic Acid
DRMI	Dropout Reason-based Multiple Imputation
EAIR	Exposure-adjusted Incidence Rate
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EOS	eosinophils
EOT	End of Treatment

EQ-5D-5L	European Quality of Life – 5 Dimensions 5 Levels Questionnaire
ER	Emergency Room
FAS	Full Analysis Set
FEF25-75%	Forced Expiratory Flow over 25-75% of the vital capacity
FEIA	Fluorescent Enzyme Immunoassay
FeNO	Fractional Exhaled Nitric Oxide
FEV ₁	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GEE	Generalised Estimating Equation
HD	High Dose
HRU	Health Resource Utilisation
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
Ig	Immunoglobulin
IP	Investigational Product
IPD	Investigational Product Discontinuation
ITT	Intent-to-Treat
IxRS	Interactive voice/web response system
L	Litre
LABA	Long-Acting Beta Agonist
LLOQ	Lower Limit of Quantification
LOESS	Locally Estimated Scatterplot Smoothing
MAR	Missing At Random
MD	Medium Dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NMAR	Missing Not At Random
nAb	Neutralizing Antibodies
NB	Negative Binomial
NC	Not Calculable
NQ	Non-quantifiable
OCS	Oral Corticosteroids

PD	Pharmacodynamic
PEF	Peak Exploratory Flow
PK	Pharmacokinetics
PPB	Parts Per Billion
PT	Preferred Term
Q4W	Every 4 Weeks
QTc	Corrected QT Interval
RNA	Ribonucleic Acid
SABA	Short-Acting Beta Agonist
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
SoA	Schedule of Assessment
TBL	Total Bilirubin
UC	Urgent Care
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
VAS	Visual Analog Scale
WHO	World Health Organisation

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	7-Nov-2022	Initial approved SAP	N/A	N/A
Data presentation	5-Feb-2025	Section 3.1: Addition of details about the Abbreviated CSR due to early study termination and which analyses will be performed	N/A	To clarify which summaries and analyses will be performed for the abbreviated CSR
Data presentation	5-Feb-2025	Section 3.2: “Enrolled” and “Safety Analysis Set” analysis population labels have been changed to “Screened Set” and “Safety Set” respectively	No (change from the protocol detailed under section 2.1)	To align with TFLs presentation company standards
Data presentations	5-Feb-2025	Section 3.3.1.5: details added about study periods presentation	N/A	To clarify study periods presentation
Data presentation	5-Feb-2025	Section 4.1.1.2: Disposition categories presentation has been updated	N/A	To align with TFLs presentation company standards

Data presentation	5-Feb-2025	Sections 4.1.1.2, 4.1.3.2, 4.1.9.2: Summaries on patients: - that discontinued treatment or withdrew from study, - with IP administration impacted, - with Important PD, related to global/country situation removed Also, summaries (section 4.5.2.2) on COVID-19 AEs removed	N/A	Not mandatory for the CSR anymore
Data presentation	5-Feb-2025	Section 4.1.1.2: Clarification on stratification factors derivation	N/A	The derivation has been adapted to cases where eosinophils counts for randomization were collected after Visit 1
Other	5-Feb-2025	Section 1 and Appendix 7.2: Updated GINA 2021 version to GINA 2022	Yes	GINA version has been updated to GINA 2022 to be consistent with latest version of CSP.
Other	5-Feb-2025	Section 3.3.1.6: India added to the list of countries in region 1.	N/A	New country has been added to the study, and therefore added in region 1 for the analysis.
Other	5-Feb-2025	Section 4.1.2.2: Analysis set presentation has been updated	N/A	To align with TFLs presentation company standards

Other	5-Feb-2025	Section 4.1.5.1 and 4.1.6.1: Updated list of baseline characteristics and baseline disease characteristics	N/A	Addition of variables of interest
Other	5-Feb-2025	Section 4.2.6.1: Updated list of other diseases presented in baseline characteristics	N/A	To be consistent with data collected in eCRF.
Other	5-Feb-2025	Summary (n, mean, SD, median, lower and upper quartile, minimum and maximum value) of the total daily ICS dose at baseline, has been removed	N/A	Not needed for CSR
Other	5-Feb-2025	Table 5 Objectives and estimands have been updated to include missing data strategy.	Yes	To clarify the distinction between missing data imputation and intercurrent events handling strategies.
Other	5-Feb-2025	Section 4.2.1.2: Table 6 updated to include derivation of Final daily maintenance OCS derivation in situations of withdrawal from study due to early termination of the study by sponsor, death and missing after IP discontinuation	No (change from the protocol detailed under section 2.1)	To encounter for additional Final daily maintenance OCS derivation Situations
Other	5-Feb-2025	Section 4.2.1.5: addition of a sensitivity analysis on primary endpoint	N/A	To examine the sensitivity of the results of the primary analysis to the use of incomplete data due to early termination of the study

Other	5-Feb-2025	Section 4.2.6.2: Corrected the time at risk derivation	N/A	To clarify the time at risk derivation.
Other	5-Feb-2025	Section 4.2.11.2: Correction of score derivation specification	N/A	Typo corrected
Data presentation	5-Feb-2025	Section 4.4: ADA variable list to be presented updated	N/A	To align with TFLs presentation company standards
Data presentation	5-Feb-2025	Section 4.5.2.2: AEs summaries list to be presented updated	N/A	To align with TFLs presentation company standards
Data presentations	5-Feb-2025	Section 4.5.2: Updated reporting (i.e., EAIR definition and risk differences)	N/A	To add clarity around AE presentations.
Other	5-Feb-2025	Fixed minor editing and spelling mistakes. Missing references added.	N/A	N/A

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D5180C00024 supporting the clinical study report (CSR).

The reader is referred to the clinical study protocol (CSP) and the electronic case report form (eCRF) for details of study conduct and data collection.

This is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the effect of tezepelumab compared to placebo on oral corticosteroid (OCS) dose reduction, whilst maintaining asthma control, in adult participants with severe, OCS-dependent asthma. The study also investigates the effects of tezepelumab on lung function, clinical markers of asthma control, including asthma exacerbation rate and patient-reported outcomes, along with biomarkers of asthma inflammation.

Approximately 207 participants aged 18-80 years are randomised to tezepelumab or placebo, in a 2:1 ratio, for a total of 7 doses. Treatment allocation is stratified by region and eosinophil counts at Visit 1 (< 150 cells/ μ L, $150 - < 300$ cells/ μ L, ≥ 300 cells/ μ L) to ensure that treatment assignment across regions and eosinophil subgroups is balanced.

Participants randomised are monitored to ensure that a maximum of 20% have an eosinophil count of < 150 cells/ μ L at Visit 1 (with a historical EOS ≥ 300 cells/ μ L within 12 months prior to Visit 1) and approximately 40% have ≥ 300 cells/ μ L at Visit 1.

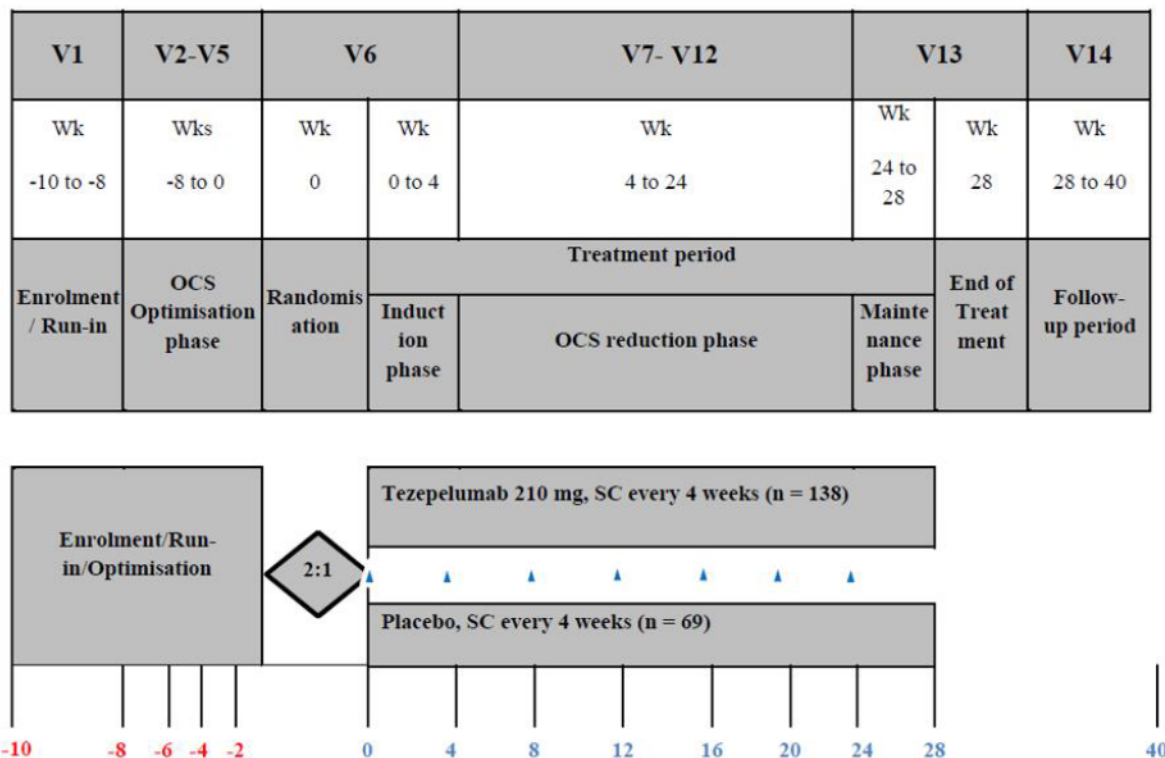
The study randomises participants treated with documented OCS maintenance therapy for at least 6 months prior to Visit 1 and who are receiving a stable dose of OCS in the range ≥ 7.5 mg to ≤ 30 mg (prednisone or prednisolone) daily or daily equivalent for at least 1 month prior to Visit 1. Participants are required to be on a medium dose (MD) or high dose (HD) ICS (as defined in GINA 2022, see Appendix 7.2) for at least 12 months prior to Visit 1 and on LABA with HD ICS for at least 3 months prior to Visit 1. Additional maintenance asthma controller medications are allowed according to standard of care practice. Their use must be documented for at least 3 months prior to Visit 1. Participants remain on their entry asthma maintenance treatments (ICS/LABA, other controllers), without any changes (except OCS), from Visit 1 until preferably 4 weeks after last dose of study intervention except during the treatment of an asthma exacerbation. Participants are required to have EOS ≥ 150 cells/ μ L at Visit 1 or a documented history of EOS ≥ 300 cells/ μ L within 12 months prior to Visit 1.

A schematic view of the study is shown on [Figure 1](#). After enrolment at Visit 1, all participants enter a 2-week run-in period and then an up to 8-week OCS optimisation phase to establish a minimum effective dose (the optimised dose) of prescribed OCS. The OCS optimisation phase may be shortened if an optimised OCS dose is determined earlier than 8 weeks or may be extended to allow for treatment of an asthma exacerbation and then permit the 2-week period of participants receiving a stable optimised OCS dose prior to

randomisation. There are 3 phases in the treatment period following randomisation (Visit 6):

- **Induction phase** – from Visit 6 (Week 0) to Visit 7 (Week 4) during which participants should remain on their optimised OCS dose.
- **OCS reduction phase** – from Visit 7 (Week 4) to Visit 12 (Week 24) during which the OCS dose reduction should be started at Visit 7, with the possibility of dose reduction every 4 weeks.
- **Maintenance phase** – from one day after Visit 12 (week 24) to the day of Visit 13 (Week 28), which is the End of Treatment visit. In this phase participants should remain on the stable maintenance OCS dose reached during the reduction phase or continue without OCS if the OCS dose was reduced to 0 mg during the reduction phase. No further reduction takes place during this phase.

Figure 1. Study design



V = Visit; Wk/Wks = week/weeks; n = number of participants; OCS = oral corticosteroids; SC = subcutaneous injection; ▲ = Study intervention administration

Participants who prematurely discontinue treatment should be encouraged to return for all regularly scheduled visits. Participants are given 3 options as to how they will be followed (CSP Section 7.1.1):

- Option 1: The participant returns for all regular clinic visits and perform all scheduled assessments until the EOT visit at Week 28 (+/-5 days).
- Option 2: The participant is offered follow-up monthly via telephone calls until the participant attends the EOT visit at Week 28 (+/-5 days) at the site. The participant completes the daily diary, performs PEF measurements and all questionnaires on the handheld device at home.
- Option 3: If the participant cannot or does not wish to comply with any of the options above (or any component of them such as only telephone-based visits without completion of the daily diary), the investigator will contact via telephone the participant at 28 weeks post-randomisation (at EOT visit) to collect AEs/SAEs, changes in concomitant medication, including OCS dose, health care utilisation, and asthma exacerbation information.

With 138 participants randomised to tezepelumab and 69 randomised to placebo it is estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint (Table 1) is approximately 90% assuming a true odds ratio of 2.5 and with the placebo assumptions based on SOURCE study (NCT03406078) (Wechsler et al, 2022) and exploratory analyses performed to assess differences in design in the current study (CSP Section 9.2). Table 1 presents 2-sided hypotheses evaluated in the trial. Multiple testing strategy is applied to strongly control type I error at 5% significance level as described in Section 3.3.4.

The list of primary and key secondary objectives and estimands is presented in Table 5.

Table 1. Hypotheses of primary and key secondary endpoint

Endpoint	Null hypotheses	Alternative hypotheses	Direction of superiority of tezepelumab is indicated by
Primary endpoint			
Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 while maintaining asthma control.	H ₀₁ : Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 28 weeks whilst not losing asthma control (tezepelumab/placebo) = 1	H ₁₁ : Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 28 weeks whilst not losing asthma control (tezepelumab/placebo) ≠ 1.	An odds ratio greater than 1.
Key secondary endpoint			
Change from baseline in pre-bronchodilator forced expiratory volume in 1 second	H ₀₂ : The difference in mean change from baseline in pre-BD FEV ₁ (L) at	H ₁₂ : The difference in mean change from baseline in pre-BD FEV ₁ (L) at	A difference greater than 0.

(pre-BD FEV ₁) at Week 28.	Week 28 (tezepelumab – placebo) = 0.	Week 28 (tezepelumab – placebo) ≠ 0.	
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2 CHANGES TO PROTOCOL PLANNED ANALYSES

2.1 Changes between Protocol and SAP planned analysis

The following change has been made to protocol planned analyses:

- “Enrolled” and “Safety Analysis Set” analysis population labels have been changed to “Screened Set” and “Safety Set” respectively, keeping the definition unchanged. The rationale for this change is to align the analysis population label to the company standards.
- The Final daily maintenance OCS derivation (Table 6) has been updated to cover additional situations such as patients withdrawing from the study prior to Week 28 due to early study termination by sponsor and subjects completed study and discontinued treatment having missing data at Week 28.

2.2 Changes to planned analysis after Sponsor decision to early terminate the study

On the **CCI** AstraZeneca decided to early terminate the study due to challenge in recruiting patients: with clinical practice shifting, there have been a decrease in long-term maintenance of OCS use for treating severe asthma, making it increasingly difficult to find patients who met the study's inclusion criteria. Therefore, the study will not reach its full sample size and as such, only a subset of the analysis will be performed, which includes the summaries and analyses listed in Table 2. Moreover, only the final DBL will be performed.

Table 2. Subset of the analyses performed for abbreviated CSR

Domains/Endpoints	Summaries/analyses performed for abbreviated CSR
Subject Disposition and Completion Status	All summaries defined under Section 4.1.1.2
Analysis Sets	All summaries defined under Section 4.1.2.2
Protocol Deviations	All summaries defined under Section 4.1.3.2
Demographics	All summaries defined under Section 4.1.4.2
Baseline Characteristics	All summaries defined under Section 4.1.5.2
Disease Characteristics	All summaries defined under Section 4.1.6.2

Medical History and Concomitant Disease	All summaries defined under Section 4.1.7.2
Prior and Concomitant Medications	All summaries defined under Section 4.1.8.2
Compliance with treatment, OCS, daily diary and home PEF, and regularly scheduled asthma inhaler	All summaries defined under Section 4.1.9.2
Primary endpoint	All summaries and statistical analysis defined under Section 4.2.1.4 Sensitivity analysis excluding early withdrawals due to early study termination defined under study 4.2.1.5
Key Secondary Endpoint – Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV1) at Week 28	Only descriptive statistics described under Section 4.2.2.4
Secondary Endpoint - Proportion of participants with 100% reduction from baseline in daily maintenance OCS dose at Week 28	Only descriptive statistics described under Section 4.2.3.4
Secondary Endpoint - Proportion of participants with daily maintenance OCS dose ≤ 5 mg at Week 28	Only descriptive statistics described under Section 4.2.4.4
Secondary Endpoint - Proportion of participants with $\geq 50\%$ reduction from baseline in daily maintenance OCS dose at Week 28	Only descriptive statistics described under Section 4.2.5.4
Secondary Endpoint - Annualised asthma exacerbation rate (AAER) over 28 weeks	Only descriptive statistics described under Section 4.2.6.4 and 4.2.6.5
Secondary Endpoint - Time to first asthma exacerbation	Only Kaplan Meier plot described under Section 4.2.7.4
Secondary Endpoint - Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) score at Week 28	Only descriptive statistics described under Section 4.2.8.4
Secondary Endpoint – Weekly mean home peak expiratory flow (PEF) (morning and evening) at Week 28	Only descriptive statistics described under Section 4.2.9.4
Secondary Endpoint - Change from baseline in AQLQ(S)+12 total score	Only descriptive statistics described under Section 4.2.10.4
Secondary Endpoint - Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score	Only descriptive statistics described under Section 4.2.11.4
Secondary Endpoint - Change from baseline in biomarkers	Only descriptive statistics described under Section 4.2.12.4
Pharmacokinetics	All summaries defined under Section 4.3
Immunogenicity	All summaries defined under Section 4.4

Exposure	All summaries defined under Section 4.5.1.2
Adverse events	All summaries defined under Section 4.5.2.2
Clinical Laboratory, Blood Sample	All summaries defined under Section 4.5.3.2
Clinical Laboratory, Urinalysis	All summaries defined under Section 4.5.4.2
Vital signs	All summaries defined under Section 4.5.5.2

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Two database locks are planned in this study. The primary DBL is conducted after all participants have completed 28 weeks of treatment, and the final DBL is conducted once all participants have completed the last safety follow-up visit at Week 40. All analyses of the primary and secondary objectives are performed based on the primary DBL data and presented in CSR. Following the final DBL, data summaries created are presented as an addendum to the CSR.

All personnel involved with the analysis and conduct of the study remain blinded until the primary DBL and important protocol deviations are identified. After primary DBL, treatment allocation for participants becomes known to the Sponsor staff and/or designated contract research organization staff. The individual participant-level blinding is maintained for the Investigator, investigational site staff, and for the participant until the final DBL.

Any deviations from this plan are reported in the clinical study report.

Analyses are performed by AstraZeneca or its representatives.

3.2 Analysis Population

The populations to be used in the analyses (as described in CSP Section 9.3) are described in the following table.

Table 3. Populations for analysis

Population/Analysis set	Description
Screened Set	All participants who sign the ICF.
Randomly assigned to study intervention	All participants randomised to study treatment (irrespective of whether treatment is subsequently taken).
Full Analysis Set (FAS)	All participants randomised to study treatment who received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study.

Population/Analysis set	Description
Safety Set	All participants who received at least one dose of study intervention.
Pharmacokinetic analysis set	All participants in the full analysis set who received tezepelumab treatment and had at least one PK blood sample collected post first dose with quantifiable serum concentration of tezepelumab which is assumed not to be affected by factors such as protocol deviations (e.g., disallowed medication or incorrect study medication received).

Efficacy analyses as well as demographics and baseline characteristics are summarised based on the full analysis set. Participants are analysed according to their randomised treatment (including in the case of any discrepancies between randomised and actual treatment).

Safety and immunogenicity presentations are based on the safety set, with participants assigned according to their actual treatment in the case of any discrepancies between randomised and actual treatment. A participant who has on one or more occasions received active (tezepelumab) treatment is assigned to the tezepelumab group, regardless of the randomised treatment assignment. A participant who has on no occasion received any active (tezepelumab) treatment is assigned to the placebo group, regardless of the randomised treatment assignment. Any important deviations from the randomised treatment assignment, and any participants that have received investigational product without being randomised is listed and considered when interpreting the safety data.

All PK summaries are based on the pharmacokinetic analysis set.

Participants who withdraw consent to participate in the study are included up to the date of their study termination. Participants who are lost to follow up are included up to the last visit date.

3.3 General Considerations

3.3.1 General Study Level Definitions

3.3.1.1 Baseline definition

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

In general, the last non-missing measurement prior to first dose of study intervention serves as the baseline measurement for safety, immunogenicity, and pharmacokinetic variables. If there is no value prior to first dose of study intervention, then the baseline value is not imputed, and is set to missing. For safety variables if no time is recorded for an assessment, and the assessment takes place at the same day as the 1st IP dose, this is assumed to be a pre-dose assessment.

The baseline OCS dose is the most recent prescribed daily maintenance OCS dose prior to randomisation and derived following rules described in Section 3.3.1.2.

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 is considered missing if either evening or following morning is missing. However, some analyses may consider morning and evening separately.

For weekly mean scores derived from participant daily diary (including, but not limited to, Asthma Symptom Diary score) and weekly means of the home-based PEF the baseline value is defined as the mean of the available data in the most recent week prior to the date of randomisation. If more than 3 days are missing in this week, then the baseline weekly mean is missing. The “most recent week” starts with the evening measurement one week prior to the date of randomisation and ends with the morning measurement on the day of randomisation.

3.3.1.2 Daily OCS dose

Unless specified otherwise, the daily maintenance OCS dose, including the daily OCS at baseline and the final daily OCS dose, is defined based on the prescribed maintenance dose of OCS, expressed as a dose per day, at the time of the relevant visit. If the participant is on a fixed daily dose, then the OCS dose is defined as that prescribed dose. If the participant is on every other day regimen (or different doses every other day), then the OCS dose is defined as the average amount prescribed to be taken each day. For example, should a participant be on a 10 mg every other day regimen of OCS, their OCS dose is defined as 5 mg.

The asthma maintenance dose of OCS is collected on the “Systemic Corticosteroids” (ECSYSCRT) eCRF page with a therapy reason of “Asthma maintenance dose”, “Titration, due to asthma” and “Sign/symptoms of AP”. The prescribed OCS dose with therapy reason of “Asthma exacerbation per protocol” or “Worsening of asthma, without exacerbation” is not included in the daily maintenance OCS dose calculation.

In case of more than one OCS dose prescribed on the same day, then the following rules should apply:

- If the therapy reason of each dose is related to the asthma maintenance OCS dose (“Maintenance dose”, “Titration, due to asthma” or “Sign/symptoms of AP”), then the sum of the doses should be calculated.
- If there is a mixture of OCS doses prescribed for asthma maintenance (“Maintenance dose”, “Titration, due to asthma” or “Sign/symptoms of AP”) and asthma worsening or exacerbation (“Worsening of asthma, without exacerbation” or “Asthma exacerbation per protocol”), then these maintenance OCS doses are not included in the calculation of daily maintenance OCS dose (i.e. when maintenance

OCS dose overlaps with the OCS burst prescribed to treat asthma worsening or exacerbation, it is considered as part of the worsening/exacerbation treatment).

3.3.1.3 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 is set to missing.

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

3.3.1.4 Bronchodilator responsiveness

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

$$\% \text{ Bronchodilator responsiveness} = \frac{[(\text{post-BD FEV}_1 - \text{pre-BD FEV}_1) / \text{pre-BD FEV}_1] * 100\%}{}$$

The post-BD FEV₁ measurement in the bronchodilator responsiveness derivation is the measurement after up to 4 SABA inhalations.

3.3.1.5 Study periods

The following study periods are defined for analysis purposes:

Enrolment / Run-in period: starts on the date of the first study procedure and ends one day prior to the start of the optimization period (Visit 2) (for randomised participants) or on the date of the last study procedure (for screening failures). If any participant is re-screened, the latest available screening is used for this purpose.

Optimization period: starts on the date of Visit 2 and ends one day prior to randomisation (for randomised participants) or on the date of the last study procedure (for screening failures). If any participant is re-screened, the latest available screening is used for this purpose.

For efficacy analyses, Run-in and Optimization periods will be presented together and referred to as Run-in period (i.e. the period that starts on date of the first study procedure and ends one day prior to randomisation).

For safety analyses, the period that starts on the date of the first study procedure and ends one day prior to date of first dose of study intervention will be referred to as Pre-treatment period.

Planned treatment period: starts on the date of randomisation and ends on the date of the Week 28 visit or earlier study withdrawal date (for participants not followed up until Week 28).

On-treatment period: starts on the date of randomisation (efficacy)/date of first dose of study intervention (safety) and ends on earliest(date of last dose of study intervention + 33 days, date of death, date of study withdrawal). The date of study withdrawal is taken from the “Disposition” eCRF page, where any status other than “Completed” has been entered.

Post-treatment period/Follow-up period: starting one day after the end date of on-treatment period, defined above for efficacy and safety analyses, respectively, and ending on the study completion or withdrawal date.

On-study period (planned treatment and follow-up period): starts on the date of randomisation (efficacy) / date of first dose of study intervention (safety) and ends on the study completion or withdrawal date. For analysis performed at primary database lock, the on-study period is understood to include all data recorded up until the date of the data cut-off for the primary database lock (which includes all follow-up data available at the time of the data cut-off).

3.3.1.6 Definition of subgroups

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

- * Eosinophils (EOS) at baseline group: < 300 cells/ μ L, ≥ 300 cells/ μ L
- * Eosinophils (EOS) at baseline group: < 150 cells/ μ L, ≥ 150 cells/ μ L
- Eosinophils (EOS) at baseline group:
 - < 150 cells/ μ L,
 - ≥ 150 cells/ μ L to < 300 cells/ μ L,
 - ≥ 300 cells/ μ L to < 450 cells/ μ L,
 - ≥ 450 cells/ μ L
- * Baseline FeNO group: < 25 ppb, ≥ 25 ppb
- Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA
 - All 11 specific IgE panels are used in the derivation, i.e., 7 panels related to perennial specific IgE status, and 4 panels related to seasonal specific IgE status
 - “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 11 panels to be available.
 - “All FEIA negative” requires all 11 specific IgE panels to be negative.
 - If there are fewer than 11 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 7 panels to be available.
 - “All perennial FEIA negative” requires all 7 specific IgE panels to be negative.
 - If there are fewer than 7 panels with data available and none of these is positive, then IgE status is considered “Unknown perennial FEIA”.
 - The 7 panels include: American Cockroach, Cat Dander, *D. farinae*, *D. pteronyssinus*, Dog Dander, German Cockroach, Mold Mix.
 - Positive is defined as a value ≥ 0.35 kU/L.
- Baseline seasonal 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”.
 - The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.
 - Positive is defined as a value ≥ 0.35 kU/L.
- Baseline body mass index (BMI): <18.5 kg/m², 18.5 to <25.0 kg/m², 25.0 to <30.0 kg/m², ≥ 30.0 kg/m²
- * Baseline body mass index (BMI): <30 kg/m², ≥ 30 kg/m²
- * Baseline daily OCS dose: ≤ 10 mg versus >10 mg prednisone or prednisolone
- * Age category: age (≥ 18 to <65 years) and age (≥ 65 years)
- * Gender: Male/Female

- Race: White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other, Multiple
- * Region: 1: Canada, USA, South Korea, Thailand, India; 2: Mexico, Brazil, Peru, Chile; 3: Czech Republic, Poland, Turkey
- Country

3.3.2 Visit Windows

Summaries and analyses, both efficacy and safety, which are presented by time point (e.g., “Week 28”) use a visit window to classify the data record, unless otherwise stated. The visit window 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 (e.g., the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

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

For efficacy variables, the reference start date is the date of randomisation, and relative day is defined as $(Date\ of\ assessment - Date\ of\ randomisation) + 1$.

For safety variables, the reference start date is the date of first dose of study intervention, and relative day is defined as $(Date\ of\ assessment - Date\ of\ first\ dose\ of\ study\ intervention) + 1$.

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

- The non-missing value closest to the target day is 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 is 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 is selected for analysis at that visit.
- If two non-missing values (for continuous variables) 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 is selected for analysis at that visit. For categorical variables in this situation, the worst case is used.

- 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 titer value should be selected.

If a participant has no value within a particular visit window, then the participant has a missing value at that visit in summaries and analysis.

The same visit window definitions below are used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.3.1.5). In practice, each data record in the planned treatment period is first identified, and then further flagged according to whether it is on-treatment or off-treatment. This flag is used to select all eligible records for subsequent visit windowing, according to whether the derived visits are to be used in a planned treatment period or an on-treatment 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.

Table 4 summarises the visit windows to be used. “Visit Window 1” corresponds to the full (mostly 4-weekly) protocol scheduling for clinic visits, including those variables which are not captured at every clinic visit, unless otherwise stated. “Visit Windows 2” summarises the visit windows which are used for EQ-5D-5L, for which more frequent completion (every 2 weeks) is scheduled in the protocol. “Visit Windows 3” presents the visit windows which are used for those variables measured less frequently. These variables are weight, AQLQ(s)+12 score, SGRQ score, post-BD spirometry and biomarkers (EOS, FeNO and total IgE).

Table 4 Visit Windows

Visit	Time Point	Target Day	Visit Window		
			1: full visit schedule	2: EQ-5D-5L	3: sparse schedule
Visit 6	Week 0	1	See Section 3.3.1.1 for baseline definitions		
	Week 2	15	-	2-21	-
Visit 7	Week 4	29	2-42	22-35	2-56
	Week 6	43	-	36-49	-
Visit 8	Week 8	57	43-70	50-63	-
	Week 10	71	-	64-77	-
Visit 9	Week 12	85	71-98	78-91	-
	Week 14	99	-	92-105	-

Visit	Time Point	Target Day	Visit Window		
			1: full visit schedule	2: EQ-5D-5L	3: sparse schedule
Visit 10	Week 16	113	99-126	106-119	-
	Week 18	127	-	120-133	-
Visit 11	Week 20	141	127-154	134-147	-
	Week 22	155	-	148-161	-
Visit 12	Week 24	169	155-182	162-175	-
	Week 26	183	-	176-189	-
Visit 13	Week 28	197	183-217	190-203	169-224
Visit 14	Follow-up	281	218-301	-	-
	Week 40				

Visit windows presented in [Table 4](#) does not apply for calculation of daily OCS dose at each timepoint. The OCS dose at each visit is based on actual visit dates to account for changes in OCS dose at scheduled visit. The visit window related to Visit X is calculated as [Visit(X-1) date + 2 days; Visit(X) date + 1 day]. For Week 28, the visit window is [Visit 12 date + 2 days; Visit 13 date].

Visit windows presented in [Table 4](#) are also not used for data captured on the handheld devices daily by the participant, which is aggregated for analysis at each relevant time point by using a weekly mean or similar approach. In general, the Week 1 starts with the evening measurement on the day of randomisation and ends with the morning measurement one week later (i.e., 7 daily pairs, where one day is defined as evening followed by morning). If more than 3 days are missing, then the Week 1 mean value is missing. Weekly mean scores for all subsequent weeks are defined similarly, with the same rule for handling missing days. More details are provided in the relevant endpoint derivation sections of this SAP.

In all cases above, no time points are presented in summary tables or included in statistical analysis which do not correspond to the time points scheduled in the protocol for the variable in question. Listings of data include all scheduled and unscheduled visits, including derived weekly means for data recorded beyond the final scheduled visit for all participants randomised.

3.3.3 Handling of Unscheduled Visits

Data collected at unscheduled visits is included in baseline definitions (as described in [Section 3.3.1.1](#) provided they remain prior to the date of randomisation (efficacy) or the date of first dose of study intervention (safety) and in analyses following the rules described in [Section 3.3.2](#)).

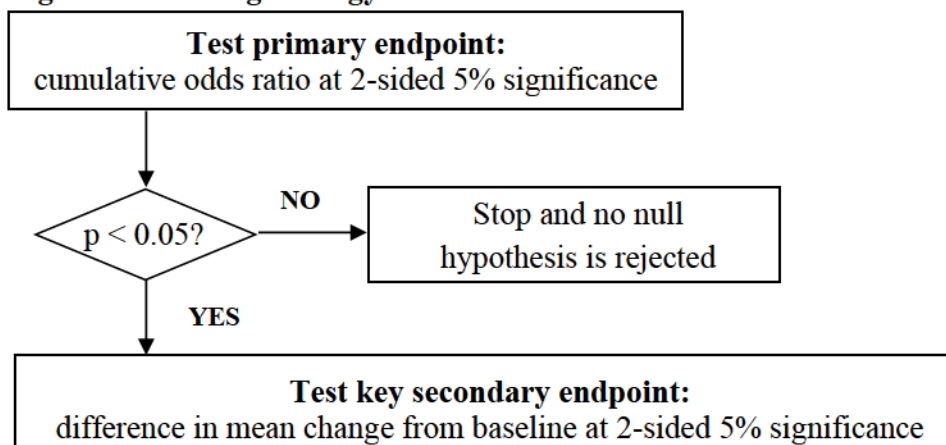
3.3.4 Multiplicity/Multiple Comparisons

In the trial the 2-sided hypotheses of primary and key secondary objectives, as presented in [Table 1](#), are verified. To account for multiplicity, the following hierarchical testing procedure is applied:

- 1 First the null hypothesis H01 is tested at a 2-sided 5% significance level with regards to the primary endpoint (categorised percent reduction from baseline in the daily OCS maintenance dose at Week 28 whilst maintaining asthma control).
- 2 If H01 is rejected, then the null hypothesis H02 is tested at a 2-sided 5% significance level with regards to the key secondary endpoint (change from baseline in pre-BD FEV₁ (L) at Week 28).

The multiple testing strategy is presented in [Figure 2](#).

Figure 2 Testing strategy



3.3.5 Handling of Protocol Deviations in Study Analysis

Only important protocol deviations (PDs) are tabulated and listed in the CSR. 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 participant's rights, safety or well-being. Important PDs in this study are grouped under one of the following categories:

- Inclusion Criteria Deviations,
- Exclusion Criteria Deviations,
- Discontinuation Criteria for study product met but participant not withdrawn from study treatment,
- Discontinuation Criteria for overall study withdrawal met but participant not withdrawn from study,
- Investigational Product (IP) Deviation,
- Excluded Medications taken,

- Deviations to study procedure,
- Other Important Protocol Deviations.

All the important PDs are identified and documented by the study team prior to unblinding of the trial at the primary database lock. As far as possible, the occurrence of important PDs is monitored (blinded) during the trial, to allow for retraining of Investigators about protocol defined methods if applicable to prevent further PDs.

Except for the PK analyses, important PDs are not used to exclude any participant from the analysis set, nor to exclude any data from participants included in an analysis set.

The study PD Plan outlines the management of PDs and includes the proposed categories of important PDs in this trial.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline and disease characteristics, medical and surgical history, prior and concomitant medication and study drug compliance.

All summaries specified in Section 4.1 are presented by treatment groups separately and combined together (“Total”).

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Disposition information and completion status are directly obtained from electronic case report form (eCRF).

Time to last dose of study intervention is derived based on the following formula, where date of last dose of study intervention is taken from the “Discontinuation of Investigational Product” eCRF page for all participants (regardless if they discontinued study intervention or not):

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

Time to premature study withdrawal is derived based on the following formula, where study withdrawal date is taken from the “Disposition” eCRF page if a participant status other than “Completed” has been entered:

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

Participants who did not prematurely withdraw from study are censored at the completion or discontinuation date from the “Disposition” eCRF page, where participant status of “Completed” has been entered. At primary DBL, ongoing participants are censored at their last visit date.

4.1.1.2 Presentation

Participant disposition is summarised using the Screened set. The number and percentage of participants within each treatment group are presented by the following categories: screened, not randomised (and reason), randomised, not treated, completed treatment, discontinued treatment (and reason), completed study (completed study intervention and study, discontinued study intervention but completed study assessments), and withdrew from study (including reason).

The number and percentage of participants, who discontinued treatment, but remained in the study are also presented by option of follow up as described in Section 1.

Participants recruitment by region, country and site is also summarised by analysis set.

Kaplan-Meier plots are produced summarising separately the time (in days) to last dose of treatment and premature withdrawal from the study.

Stratification factors recorded at randomisation in the IxRS and as recorded from external vendor are summarised for the FAS. For deriving the eosinophil count strata (<150 cells/uL, >=150-<300 cells/uL, >=300 cells/uL) analysed by the external vendor, the first collected before randomization continuous value will be used.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Definitions of analysis populations are provided in Section 3.2.

4.1.2.2 Presentation

The number of participants included in the Randomised set is summarised. Moreover, the number of participants included or excluded from the Safety set, the FAS and the PK set is summarised. Reasons why participants are excluded from a specific analysis set is also presented in the table and listed.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Categories of Important Protocol deviations are described in Section 3.3.5. Further details regarding definitions of important protocol deviations are provided in Protocol Deviations Plan.

4.1.3.2 Presentation

Only important protocol deviations are summarised. The number and percentage of participants with at least one important protocol deviation as well as for each important protocol deviation category is described. Information of participants with important protocol deviation is also listed.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demography information (age, gender, race, and ethnicity) is directly obtained from electronic Case Report Form (eCRF). Age is derived from the date of informed consent-date of birth, rounded down to the nearest integer. In addition, participants are classified based on age group (≥ 18 to < 65 years, ≥ 65 years).

4.1.4.2 Presentation

Demographics are summarised using frequency counts and percentages (for categorical variables) and descriptive statistics (n, mean, standard deviation, median, minimum and maximum) (for continuous variable).

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include, but may not be limited to:

- weight (kg), height (cm), BMI (kg/m^2) calculated as weight (kg) divided by height (m^2) and BMI categorised as described in Section [3.3.1.6](#)
- smoking status
- history of allergy (any allergy, allergen class)
- lung function assessments at the clinic
- home-based assessments of PEF (weekly mean morning and evening PEF (L/min))
- asthma control and asthma-related quality of life questionnaires (ACQ-6, AQLQ(s)+12, SGRQ)
- biomarkers: eosinophils ($\text{cells}/\mu\text{L}$), eosinophils categorised as described in Section [3.3.1.6](#), FeNO (ppb), FeNO categorised as described in Section [3.3.1.6](#), total IgE (IU/mL) and categorised as defined in Section [3.3.1.6](#)
- IgE (IU/mL), (Any) specific IgE status (FEIA), perennial specific IgE status (FEIA) and seasonal specific IgE status (FEIA) as defined in Section [3.3.1.6](#)

- Daily OCS dose at baseline absolute values (mg) and categorised as in Section [3.3.1.6](#)

4.1.5.2 Presentation

Baseline characteristics are summarized in a similar manner as described in Section [4.1.4.2](#).

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Baseline disease characteristics include, but may not be limited to:

- age at asthma diagnosis, defined as = asthma diagnosis year – year of birth + 1
- time since asthma diagnosis (years), defined as date of randomisation – date at asthma diagnosis + 1
- history of asthma exacerbations in last 24 months
- admission to ICU in the last 36 months (for asthma, for respiratory failure)
- any bronchial thermoplasty in last 36 months
- other diseases: rhinitis, allergic rhinitis, nasal polyps, chronic sinusitis, gastroesophageal reflux, aspirin exacerbated respiratory disease, acute respiratory failure, childhood asthma, chronic idiopathic urticaria, eosinophilic esophagitis, hyper eosinophilic syndrome, NSAID exacerbated respiratory disease, obesity, asthma-COPD overlap syndrome.

4.1.6.2 Presentation

Asthma characteristics are summarized in a similar manner as described in Section [4.1.4.2](#).

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history information can be directly obtained from eCRF. In case of a partial diagnosis date, if both the month and the year are available then the 1st is imputed for the day, unless the date of birth is within the same month and year (where date of birth is available, which is not the case in all countries). In this case, the date of birth is imputed instead. If only the year is available, 1st January is imputed, unless the date of birth is within that same year (where date of birth is available). In this case, the date of birth is imputed instead.

4.1.7.2 Presentation

Prior and current medical history is summarised by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by the Medical Dictionary for Regulatory Activities (MedDRA) dictionary using frequency counts and percentage of participants in

the FAS. For each PT, the number and percentage of participants reporting at least one occurrence are presented, i.e., multiple occurrences of a medical history for a participant are counted only once.

Specific surgical histories are summarised by SOC and PT, separately from medical history.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

The medications are captured on the following eCRF forms: “Concomitant Medications” (CM), “Medication of Interest” (MINT), “Systemic Corticosteroids” (ECSYSCRT) and in addition the marketed or investigational biologics taken by a participant for treatment of asthma within 12 months prior to Visit 1 are captured on “Concomitant Medications 1” (CM1).

Medications taken by any participant at any time during the study are coded using the ATC classification system within the WHO Drug Dictionary.

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

- Prior medications: end date $\leq$ date of first dose of study intervention
- Concomitant medications during on-treatment period:
 - end date $>$ date of first dose of study intervention and start date $\leq$ earliest(date of last dose of study intervention + 33 days; date of death, date of study withdrawal), or
 - end date ongoing and start date $\leq$ earliest(date of last dose of study intervention + 33 days, date of death, date of study withdrawal)
- Concomitant medications during post-treatment period (for participants still being followed up then): start date $>$ date of last dose of study intervention + 33 days

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 study intervention was still being taken). Specifically, a concomitant medication which started on-treatment and ended post-treatment is only considered on-treatment.

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 Section 6.5. They are defined following a physician review (prior to primary database lock) of the unique combinations of ATC code classifications and generic terms captured.

If the medication record has a completely missing onset date, the participant is 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 study intervention treatment, it is 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 study intervention treatment, it is assumed to have started before treatment.

If the medication record has a completely missing end date, the participant is 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 study intervention treatment, it is 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 study intervention treatment, it is assumed to have ended post-treatment.

4.1.8.2 Presentation

The number and percentage of participants receiving each medication, captured on the two eCRF forms: “Concomitant Medications” (CM) and “Medication of Interest” (MINT), is presented by ATC classification system codes and generic name. Separate tables are shown for medications received during each of the following periods: prior, concomitant (on-treatment), concomitant (post-treatment) as defined in Section 4.1.8.1. Allowed and disallowed medications are presented separately.

Data captured on “Systemic corticosteroids” (ECSYSCRT) is summarised as follows:

- The number and percentage of participants receiving allowed systemic corticosteroids (prescribed for any reason) during the on-treatment period is summarised by route, ATC code, and generic term of administration.
- The number and percentage of participants receiving disallowed systemic corticosteroids (prescribed for any reason) from Visit 1 onwards is summarised by route, ATC code, and generic term of administration.
- The total number of days of systemic corticosteroid treatment associated with asthma exacerbations per participant from the first day of study intervention up to Week 28 is presented.
- A summary (n, mean, SD, median, lower and upper quartile, minimum and maximum value) of the daily OCS dose at Visit 1 and at baseline is produced.
- In addition, a shift table of the daily OCS dose at study entry to baseline OCS dose is produced.

Data captured on “Concomitant Medications 1” (CM1) is summarised as follows:

- The number and percentage of participants who took biologics for asthma within 4 months or 5 half-lives prior to visit 1 and stopped prior to treatment (by ATC classification system codes and generic name) is presented
- The number and percentage of participants who stopped taking biologics for asthma more than 4 months or 5 half-lives prior to visit 1 (by ATC classification system codes and generic name) is presented

In addition, the number and percentage of participants treated with ICS and OCS is displayed descriptively at Visit 1 and at baseline. The summaries include also the total daily ICS dose categorised as medium or high (details provided in Appendix 7.2) and additional maintenance asthma medications.

Medications are classified using the latest version of the WHO Drug Dictionary.

All summaries are presented by treatment arm using FAS. Percentages are calculated relative to the number of participants in the FAS.

4.1.9 Compliance with treatment, OCS, daily diary and home PEF, and regularly scheduled asthma inhaler

4.1.9.1 Definitions and Derivations

Treatment compliance is calculated as:

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

In order to allow for participants who discontinue study intervention early in the compliance calculation, the number of expected dosing occasions is calculated as the number of scheduled dosing visits up to and including the last available dosing visit for that participant.

OCS compliance is calculated as:

*OCS compliance = total days compliant / total days in period * 100%.*

A participant is considered compliant with OCS if they took their OCS dose, OCS dose was not scheduled, or their OCS dose was reduced to zero on that day, as recorded in their daily diary.

Compliance with daily diary (Asthma Symptom Diary, global asthma symptom score item, rescue medication use, and night-time awakenings) and home PEF, is calculated weekly and over 28 weeks planned treatment following formula:

Compliance with daily diary and home PEF

$$= \frac{\text{number of days with at least one non – missing morning diary record} \\ \text{and at least one non – missing evening diary record}}{\text{number of days in the period}} * 100\%$$

where:

- the non-missing morning and evening values do not have to be related to the same daily diary or home PEF measurement, e.g., a participant is count as compliant at a given day if there is a non-missing measurement of global asthma symptom score in the evening and a non-missing measurement of home PEF measurement in the morning following day
- period for weekly compliance is derived as in Section 3.3.2
- period for overall compliance is defined as follows: earliest(last measurement date on daily diary or home-based PEF; end date of planned treatment as defined in Section 3.3.1.5, date of IPD visit if a participant discontinues study intervention and follows option 3).

Compliance with regularly scheduled asthma inhaler is calculated as:

*Compliance with regularly scheduled ICS/LABA asthma inhaler = number of days where question “Asthma medication taken yesterday” is marked as “Yes, I took all doses as scheduled” / number of days in the period * 100%.*

where:

- period for weekly compliance is derived as in Section 3.3.2
- period for overall compliance is defined as follows: earliest(last measurement date on daily diary; end date of planned treatment as defined in Section 3.3.1.5, date of IPD visit if a participant discontinues study intervention and follows option 3).

4.1.9.2 Presentation

Study treatment compliance and OCS compliance over 28 weeks of planned treatment period are summarised using descriptive statistics (n, mean, SD, median, lower and upper quartile, minimum and maximum value) and presenting the number and percentage of participants with compliance <70% or ≥70%. In addition, OCS compliance is also calculated for the OCS optimisation phase.

Compliance with the regularly scheduled ICS/LABA asthma inhaler as recorded in the daily diary is summarised by each week, together with the compliance with daily diary and home-based PEF using descriptive statistics (n, mean, SD, median, lower and upper quartile, minimum and maximum value).

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Table 5 includes description of primary and key secondary objectives and estimands.

Efficacy analyses are based on the Full analysis set, safety and immunogenicity presentations are based on the safety set and PK summaries are based on the pharmacokinetic analysis set as described in Section 3.2.

All summaries are presented by each treatment groups separately.

Table 5. Primary and Key secondary Objectives and estimands

Endpoint(s)	Details in section	Intercurrent event strategy	Missing data strategy(ies)	Population level summary (analysis)
Primary objective: To evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA				
Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control	4.2.1.4	- Treatment discontinuation or change in background therapy (other than OCS): all data up to Week 28 is included in the analysis (treatment policy strategy). - Initiation of therapy with biologic for treatment of asthma: final dose for analysis is defined as the OCS dose achieved prior to initiation of another biologic for treatment of asthma, increased by one dose level (composite strategy). - Death: final OCS dose for the analysis is set to baseline value	Missing data strategy for the final OCS dose at Week 28 is detailed in Table 6	Cumulative odds ratio (tezepelumab/placebo) with 95% CI
Key secondary objective: To evaluate the effect of tezepelumab compared with placebo on pre-BD lung function in participants with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA				
Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV ₁) at Week 28.	4.2.2	- Treatment discontinuation or change in background therapy (other than OCS): all data up to Week 28 is included in the analysis (treatment policy strategy). - Death or initiation therapy with another biologic for treatment of asthma: post intercurrent event data is imputed assuming an unfavourable outcome (composite strategy).	Multiple imputation assuming Missing at Random (MAR)	The difference in means (tezepelumab – placebo) with 95% CI

4.2.1 Primary Endpoint - Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control

4.2.1.1 Definition

The primary endpoint is the categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 whilst maintaining asthma control. The categories are as follows:

- Category 1: $\geq 90\%$ to $\leq 100\%$ reduction
- Category 2: $\geq 75\%$ to $< 90\%$ reduction
- Category 3: $\geq 50\%$ to $< 75\%$ reduction
- Category 4: $> 0\%$ to $< 50\%$ reduction
- Category 5: no change or any increase.

4.2.1.2 Derivations

Percent change from baseline in the final daily OCS dose at Week 28 while not losing asthma control is defined as:

$$((\text{final daily OCS dose} - \text{baseline daily OCS dose}) / \text{baseline daily OCS dose}) * 100\%.$$

The derived percent change is categorized into five categories as presented in Section 4.2.1.1. In the case of death, the category 5 (no change or any increase) is assigned regardless of the observed percentage reduction. The baseline daily OCS dose is defined in Section 3.3.1.1. The final daily OCS dose at Week 28 is derived as in Section 3.3.1.2 and Table 6. Strategies of handling intercurrent events are presented in Section 4.2.

Table 6. Final daily maintenance OCS derivation

Situation	Final daily maintenance OCS dose
Initiation of therapy with another biologic for treatment of asthma	Last reported OCS dose ^a received by participant with asthma stability verified ^b prior to initiation of another biologic for treatment of asthma and increased by one dose level (as presented in Table 7).
Death	Baseline daily OCS dose.
Premature withdrawal from the study prior to Week 28 due to early study termination by sponsor	Last reported OCS dose ^a received by participant with asthma stability verified ^b at the time of study withdrawal
Premature withdrawal from the study ^b prior to Week 28 due to any other reasons	Last reported OCS dose ^a received by participant with asthma stability verified ^b at the time of study withdrawal, increased by one dose level (as presented in Table 7).

Situation	Final daily maintenance OCS dose
Completed study and treatment discontinued subject having missing data at Week 28	Last reported OCS dose ^a received by participant with asthma stability verified ^b increased by one dose level
Any other situation	Last reported OCS dose ^a received by participant with asthma stability verified ^b

^a Daily OCS dose is based on information collected in ECSYSCRT eCRF.

^b Asthma stability is defined as no change in OCS dose for at least 2 weeks

Table 7. OCS dose titration

Latest OCS dose	Increment
≤10 mg	2.5 mg
>10 mg	5 mg

4.2.1.3 Handling of Dropouts and Missing Data

Participants may be missing specific data points for a variety of reasons. In general, data may be missing due to a participant's early withdrawal from study, lost to follow up, a missed visit, or inability to evaluate an endpoint at a particular point in time, e.g. participants who died.

[Table 6](#) contains the imputation rules for any situation leading to missing data.

4.2.1.4 Primary Analysis of Primary Endpoint

The number and proportion of participants in each of the response (dose reduction) categories is tabulated and the bar graph of the proportion of participants in each of the categories is presented.

The primary endpoint in the tezepelumab group is compared to that in the placebo group using a proportional odds (ordinal logistic regression) model with respect to categories defined in Section 4.2.1.1. The proportional odds model is used to test the hypothesis described in [Table 1](#) and to estimate the treatment effect (cumulative odds ratio) and its 95% confidence interval.

The response variable in the model is the ordered category number (1-5) at Week 28 as defined in Section 4.2.1.1. Treatment and region are included as categorical covariates, and baseline OCS dose and logarithm of baseline blood eosinophil counts are included as continuous covariates in the model.

For the 5 ordered categories defined in Section 4.2.1.1, there are 4 possible cumulative odds for each treatment group, corresponding to the 4 different possible binary splits, which are defined as follows:

- Category 1 versus categories (2,3,4,5)
- Categories (1,2) versus categories (3,4,5)
- Categories (1,2,3) versus categories (4,5)
- Categories (1,2,3,4) versus category 5.

The model assumes that the 4 possible odds ratios between the 2 treatments are the same (this is the proportional odds assumption). The validity of the proportional odds assumption across the categories of the response variable for the covariates fitted in the model is assessed by plotting empirical logits for each predictor separately. A score test statistics is also calculated, but as it is known to be liberal (Peterson et al 1990), it is interpreted with caution, and used together with the empirical logit plots to decide if the proportional odds assumption is valid.

If the proportional odds assumption is not satisfied due to non-proportional effects of region, baseline OCS dose or log baseline eosinophil counts across the response, then a partial proportional odds model is fitted, using the UNEQUALSLOPES option within SAS, to allow different effects across the categorical response for covariates shown to be non-proportional. Results of the proportional odds model and Wilcoxon rank sum test stratified by region (van Elteren test) are presented regardless of the satisfaction of proportional odds assumption of treatment across the response. If the proportionality assumption is not satisfied due to non-proportional effect of treatment, then the analysis is confirmed using a Wilcoxon rank sum test stratified by region, as described in Section 4.2.1.6.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

To examine the sensitivity of the results of the primary analysis to the use of incomplete data due to early termination of the study, the primary analysis described under section 4.2.1.4 will be repeated excluding the subset of subjects that withdrew from the study due to early study termination by sponsor.

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions about missing data, the multiple imputation methods such as pattern mixture model assuming Missing at random (MAR) or Missing not at random (MNAR) / Dropout reason multiple imputation (DRMI) is utilised.

Note that participants with missing baseline data are excluded from these analyses.

The following steps are taken to generate completed datasets up to Week 28 and perform the analyses:

Step 1: Data collected after the initiation of another biologic for treatment of asthma is set to missing.

Step 2: Non-monotone (intermediate visits) missing values imputation

The non-monotone (intermediate visits) missing values are imputed first assuming MAR. A Markov chain Monte Carlo (MCMC) method is used to partially impute the data using SAS PROC MI.

A single Markov chain is used with a non-informative (Jeffreys) prior distribution. The first 200 iterations are discarded to allow for convergence to a stationary distribution and to remove the effect of the starting values (“burn-in”). A gap of 100 iterations is used between imputations to ensure independence between imputations (“thinning”). Convergence of the MCMC algorithm is assessed. Non-monotone missing data are expected to be relatively infrequent.

Step 3: Monotone imputation of remaining missing data

The remaining monotone missing values at each visit are imputed using the sequential regression method (using the MONOTONE REG option of in PROC MI). At each iteration, missing values are imputed sequentially, one time-point at a time.

The sequential monotone regression method is achieved by including only selected data at each stage of the imputation. This is implemented as follows, where t represents each post-baseline visit, proceeding one visit at a time from the first post-baseline visit until the imputed dataset has complete values at all post-baseline visits.

If a negative OCS dose value is imputed at any time, it is replaced with a zero value.

Imputation of the monotone missing data is performed twice depending on assumed mechanisms of missingness:

- MAR: Missing data in each arm is imputed assuming the distribution within that treatment group
- MNAR/DRMI: Missing data is imputed differently depending on the reason for the dropout. Missing data for participants in the tezepelumab arm who dropped out for a treatment-related reason is imputed assuming the participant’s whole distribution, both pre-withdrawal and post-withdrawal, is the same as the placebo arm (the “copy reference” approach described in O’Kelly and Ratitch, 2014), whereas the remaining participants are imputed assuming MAR.

To impute missing values at time t for participants in the tezepelumab arm who withdrew from the study for treatment-related reasons or discontinued study intervention following option 3 (regardless of the reason of discontinuation of study intervention), the imputation model uses only placebo participants who had observed data at time t ; the dataset itself also needs to include the tezepelumab participants who withdrew for treatment-related reasons at time $t-1$, since it is these participants for which the imputation is required.

To impute missing values at time t for participants in the tezepelumab arm who withdrew from the study for reasons unrelated to treatment and for all placebo

participants, the imputations are performed assuming MAR. It means that an imputation model uses participants who had observed data at time t from the respective treatment group.

Table 8 shows how, for tezepelumab participants who withdrew from study, each possible reason for study intervention discontinuation is handled in the multiple imputation analyses assuming MNAR/DRMI. The rules in the table are applied irrespective of the length of time between discontinuing study intervention and withdrawing from study.

Table 8 Treatment assignment in DRMI imputation for tezepelumab arm

Reason for study withdrawal	Reason for discontinuation of study intervention	Treatment arm used in DRMI
• Death	• Death	Placebo
• Loss to follow up • Withdrawal by subject • Other	• Adverse event • Development of study-specific discontinuation criteria • Severe non-compliance to protocol	Placebo
	• Participant lost to follow-up • Participant decision • Other	Placebo by default (pending blinded review of any further information)
• Study terminated by Sponsor • Site terminated by Sponsor		Tezepelumab

A blinded review of participants who withdrew from study and discontinued study intervention for reasons of “Participant lost to follow-up”, “Participant decision” or “Other” are performed by the study team prior to primary database lock. A listing of these participants and the assumptions made under DRMI is documented prior to primary database lock. If any recorded comments (on either of the “Discontinuation of Investigational Product” or “Disposition” eCRF pages) indicate clearly that the reason for study withdrawal was not related to treatment, then the “Placebo” default for DRMI in the above table may be changed for that participant.

For each of the MAR and DRMI analyses, 100 imputations are carried out. A random seed of 670376 is used for the non-monotone imputations, and a random seed of 966654 is used for the monotone imputations.

The imputation model uses the OCS dose at the visit as the response variable and include treatment, region, baseline OCS dose, the OCS dose at all prior (post-baseline) visits and logarithm of baseline blood eosinophils counts.

Step 4: Analysis of complete datasets

For each of the imputed datasets:

- If a participant initiated another biologic for treatment of asthma, then the imputed OCS dose at Week 28 is set to missing and the final OCS dose at Week 28 is derived as presented in Section 4.2.1.2
- If a participant withdrew from study early, then the imputed OCS dose at Week 28 is used in the analysis as a final OCS dose at Week 28,
- In all other cases, the final OCS dose is derived as presented in Section 4.2.1.2.

The analysis of each of these datasets is as described for the primary analysis in Section 4.2.2.4. The results from the analysis of each imputed datasets are then combined across imputations in a way which appropriately accounts for within-imputation and between-imputation variance using SAS procedure PROC MIANALYZE, and results presented as per the primary analysis.

4.2.1.6 Supplementary Estimands of the Primary Endpoint

Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 while maintaining asthma control using on-treatment data

The intercurrent events such as change in background therapy (other than OCS), subject death and initiate therapy with another biologic for treatment of asthma are handled in the same way as described for primary analysis of primary endpoint. The composite strategy is applied to the intercurrent event of treatment discontinuation.

The final daily OCS dose for participants prematurely discontinuing study intervention (regardless of chosen option) is the last reported OCS dose received by participant when asthma stability was verified, at the time of study intervention discontinuation, increased by 1 dose level, as described in Table 7. The derivation of the final daily OCS dose for any other participant is following the rules described in Table 6.

The analysis specified in Section 4.2.1.4 is repeated using on-treatment data only, where the definition of on-treatment is given in Section 3.3.1.5.

Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 while maintaining asthma control using van Elteren test

The same strategies for intercurrent events are applied for the analysis as for the primary analysis of primary endpoint.

The categorised percentage reduction in daily OCS dose at Week 28, as described in 4.2.2.1, is compared between treatment arms using a Wilcoxon rank sum test stratified by region (van Elteren test).

Percentage reduction from baseline in the daily maintenance OCS dose at Week 28 while maintaining asthma control

The same strategies for intercurrent events are applied for the analysis as for the primary analysis of primary endpoint.

The absolute values and the changes from baseline in daily OCS dose are summarised descriptively (n, mean, SD, median, minimum and maximum) over time. The daily OCS dose at Visit X is the latest OCS dose during this visit. Note the visit windows for daily OCS dose per visits are based on actual visit dates as described in Section 3.3.2.

In addition, the mean (± 1 SE) and the median ($\pm 95\%$ CIs using a distribution free procedure) percentage reduction from baseline in daily OCS dose are also presented graphically over time. A LOESS plot is produced for percentage reduction from baseline in final daily OCS dose at Week 28 and logarithm of each of the continuous biomarker variables (baseline eosinophils [cells/ μ L], baseline FeNO [ppb] and baseline total serum IgE [IU/mL]).

The median value for each treatment arm is presented with a 95% confidence interval, calculated using a distribution free procedure. The median difference in the percentage reduction of daily OCS dose between tezepelumab and placebo arm and corresponding 95% CI is derived using unadjusted bootstrap approach as suggested by Keene (2019).

The percent reduction from baseline in daily OCS dose while maintaining asthma control at Week 28, described in 4.2.1.2, is compared between treatment groups using a Wilcoxon rank sum test stratified by region (van Elteren test). The p-value is presented.

Categorised percent reduction from baseline in the daily maintenance OCS dose at Week 28 while maintaining asthma control, including oral systemic corticosteroids used for reasons other than asthma

The same strategies for intercurrent events are applied for the analysis as for the primary analysis of primary endpoint.

The baseline daily OCS dose is defined in Section 3.3.1.1, and the final daily OCS dose at Week 28 is derived as in Section 3.3.1.2 and Table 6, including additional reasons of “Non-asthma condition” and “Other”. The percent change from baseline in the final OCS dose is calculated as described in Section 4.2.1.2 and categorised as presented in Section 4.2.1.1.

The endpoint is analysed similarly to the primary analysis of primary endpoint derived in Section 4.2.1.4.

4.2.1.7 Subgroup Analyses of Primary Endpoint

The number and proportion of participants in each of the response (dose reduction) categories is tabulated in each categorical baseline or demographic variables as detailed in Section 3.3.1.6.

To explore the treatment effect across subgroups a similar model is fitted as for the primary analysis with additional factors for the relevant subgroup variable and its interaction with treatment. The estimate of the treatment effect and its 95% CI within each of the subgroup categories is presented. A p-value for the treatment by subgroup interaction is not presented for each of these models due to the various difficulties in interpretation. If any of the subgroups have fewer than 10 participants in one or both treatment groups, this subgroup level is not included in the model. If that leaves only one subgroup level, the model is not fitted for that categorical variable.

4.2.2 Key Secondary Endpoint – Change from baseline in pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV₁) at Week 28

4.2.2.1 Definition

Pre-BD FEV₁ is determined by spirometry at the clinic visit. The effect of tezepelumab compared with placebo on the change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV₁) is evaluated.

4.2.2.2 Derivation

According to the CSP the maximum number of efforts for spirometry measurement is 8. The measurement used in the analysis is the one marked with Best Result Flag equal to “Yes” as per Data Transfer Specification.

Only the assessments collected at visits where pre-BD FEV₁ assessment is mandatory for all participants (Visits 6, 7, 8, 10, 13 and IPD) is used in the statistical analyses.

Data collected after initiation of therapy with another biologic for treatment of asthma are:

- set to missing for the purpose of descriptive summary
- imputed assuming an unfavourable outcome for the purpose of statistical model.

The derivation of a change from baseline in pre-BD FEV₁ at any post-baseline time point is described in Section 3.3.1.3. Baseline value is defined in Section 3.3.1.1.

4.2.2.3 Handling of Dropouts and Missing Data

The examples of missing data are provided in Section 4.2.1.3. For the purpose of statistical analysis post intercurrent event of initiation of another biologic for treatment of asthma is imputed assuming an unfavourable outcome. Other missing data is imputed assuming MAR.

4.2.2.4 Primary Analysis of Key Secondary Endpoint

The absolute values and changes from baseline in pre-BD FEV₁ are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

The following steps are taken to generate completed datasets up to Week 28 and to perform the analysis:

Step 1: Data collected after the initiation of another biologic for treatment of asthma is set to missing.

Step 2: Multiple Imputation of missing data

For participants who initiate another biologic for the treatment of asthma or died, data points after the initiation or death will be imputed assuming an unfavorable outcome. For other intercurrent events, a treatment policy strategy will be applied utilizing all available data including data collected post the intercurrent events, with missing data assumed to be missing at random. Other missing data (i.e., not following ICE) at the mandatory post randomisation visits will be imputed using a multiple imputation (MI) approach assuming missing at random.

Step 3: Analysis of complete datasets

Following the imputation steps, each of the imputed datasets is analysed using an analysis of covariance (ANCOVA) model. The response variable in the model is the change from baseline at Week 28. Treatment and region are included as categorical covariates and baseline pre-BD FEV₁ and log baseline blood eosinophil counts are included as continuous covariates in the model. Rubin's rule is applied to combine analysis results (point estimates and standard errors) from the imputed datasets.

The above model will be repeated for the following weeks: 4, 8 and 16.

The adjusted mean changes from baseline for each treatment arm together with its 95% confidence interval, as well as the mean difference with 95% confidence interval (CI) at weeks 4, 8, 16 and 28 are provided. The results are tabulated and in addition the adjusted means are displayed graphically over time.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions about missing data, multiple imputation method assuming Missing not at random (MNAR) / Dropout reason multiple imputation (DRMI) is utilised.

The analysis follows the same steps as for primary analysis of the key secondary endpoint (as presented in Section 4.2.2.4) but the missing data is imputed differently depending on the reason for the dropout.

Each of the imputed datasets is analysed using the same model specified in Section 4.2.2.4. The adjusted mean changes from baseline for each treatment arm together with its 95% confidence interval, as well as the mean difference with 95% confidence interval (CI) at each time point are tabulated.

4.2.2.6 Supplementary Analyses of the Key Secondary Endpoint

A LOESS plot is produced for change from baseline in pre-BD FEV₁ at Week 28 and logarithm of each of the continuous biomarker variables (baseline eosinophils (cells/ μ L), baseline FeNO (ppb) and baseline total serum IgE (IU/mL).

The analyses specified in Section 4.2.2.4 are repeated using on-treatment data only, where the definition of on-treatment is given in Section 3.3.1.5.

4.2.2.7 Subgroup Analyses of Key Secondary Endpoint

The absolute values and changes from baseline in pre-BD FEV₁ are summarised descriptively (n, mean, SD, median, minimum and maximum) over time by subgroups, as detailed in Section 3.3.1.6, irrespective of how few participants there are in any particular subgroups.

To explore the treatment effect on pre-BD FEV₁ across categorical baseline or demographic variables as detailed in Section 3.3.1.6, a similar steps are followed as described in Section 4.2.2.4. The similar model is fitted as for the primary analysis with additional factors for the subgroup variable and the treatment by subgroup interaction. This model is used to estimate the treatment effect and its 95% CI within each of the subgroup categories at Week 28, which is tabulated and presented graphically using a forest plot. A p-value for the treatment by subgroup interaction at Week 28 is not presented for each of these models due to the various difficulties in interpretation. If any of the subgroups have fewer than 10 participants in one or both treatment groups (with data at any post-baseline time point, not necessarily at Week 28), this subgroup level is not included in the model. If that leaves only one subgroup level, the model is not fitted for that categorical variable. If it leaves more than one subgroup level, the model is fitted using the remaining subgroups which have 10 or more participants in both treatment groups.

4.2.3 Secondary Endpoint - Proportion of participants with 100% reduction from baseline in daily maintenance OCS dose at Week 28

4.2.3.1 Definition

The percent reduction from baseline in the daily OCS dose at Week 28 whilst maintenance asthma control is categorised into binary groups depending whether a participant reduced the OCS dose to 0 mg or not.

4.2.3.2 Derivation

The derivation of percent change from baseline in daily maintenance OCS dose, baseline and final daily OCS dose is presented in Section 4.2.1.2.

For each treatment group, the number of participants with the final daily OCS dose of 0 mg is calculated. The proportion of such participants is calculated for each treatment group as:

Number of participants with final daily OCS dose equal to 0 mg / number of participants in treatment group

4.2.3.3 Handling of Dropouts and Missing Data

The same approach of handling dropouts and missing data applies as for primary endpoint (Section 4.2.1.3).

4.2.3.4 Primary Analysis

The number and proportion of participants with 100% reduction from baseline in daily OCS dose at Week 28 is presented.

The proportion of participants with 100% reduction from baseline in daily OCS dose at Week 28 is analysed using a logistic regression model. The response variable in the model is the binary status showing whether a reduction from baseline in daily OCS dose at Week 28 for a participant achieved 100% (status=1) or not (status=0). Treatment and region are included as factors in the model, and baseline OCS dose and log baseline blood eosinophil counts as a continuous (linear) covariate. An odds ratio and 95% confidence interval estimated from the model are presented.

4.2.4 Secondary Endpoint - Proportion of participants with daily maintenance OCS dose ≤ 5 mg at Week 28

4.2.4.1 Definition

Participants are categorised into binary groups depending on whether they reduced the OCS dose to ≤ 5.0 mg or not.

4.2.4.2 Derivation

The derivation of the final OCS dose at Week 28 is presented in Section 4.2.1.2.

For each treatment group, the number of participants with final daily OCS dose ≤ 5 mg is calculated. The proportion of such participants is calculated for each treatment group as:

Number of participants with final daily OCS dose ≤ 5.0 mg / number of participants in treatment group

4.2.4.3 Handling of Dropouts and Missing Data

The same approach of handling dropouts and missing data applies as for primary endpoint (Section 4.2.1.3).

4.2.4.4 Primary Analysis

The number and proportion of participants with a final daily OCS dose of ≤ 5 mg at Week 28 is presented.

The proportion of participants with a final daily OCS dose of ≤ 5 mg at Week 28 is analysed using a logistic regression model as described for the proportion of participants with 100% reduction in OCS in Section 4.2.3.4. The response variable in the model is the binary status showing whether a final daily OCS dose at Week 28 is ≤ 5 mg (status=1) or not (status=0).

4.2.4.5 Additional Analyses

The number and proportion of participants who

- were able to reduce their final daily OCS dose to ≤ 5 mg but unable to withdraw the OCS completely (reduction to 0 mg) due to adrenal insufficiency,
- were able to reduce their final daily OCS dose to ≤ 5 mg but unable to withdraw the OCS completely (reduction to 0 mg) due to adrenal insufficiency or who reached 100% reduction in final daily OCS dose (i.e., final daily OCS dose of 0 mg)

is presented.

If there are a number of participants with a final daily OCS dose of ≤ 5 mg and unable to reduce to 0 mg due to adrenal insufficiency (response variable), then a logistic regression model as described in Section 4.2.3.4 may also be performed. The response variable in the model is the binary status showing whether a final daily OCS dose at Week 28 is ≤ 5 mg and a participant was unable to reduce to 0 mg due to adrenal insufficiency (status=1) or not (status=0).

In addition, the analysis (as described in Section 4.2.3.4) is performed based on the proportion of participants with a final daily OCS dose of ≤ 5 mg and unable to reduce to 0 mg due to adrenal insufficiency and participants with 100% reduction in final daily OCS dose (i.e., final daily OCS dose of 0 mg). The response variable in the model is the binary status showing whether a final daily OCS dose at Week 28 is ≤ 5 mg and a participant was unable to reduce to 0 mg due to AI or whether the reduction from baseline in final OCS dose for the participant is equal 100% (status=1), or whether none of it is met (status=0).

4.2.5 Secondary Endpoint - Proportion of participants with $\geq 50\%$ reduction from baseline in daily maintenance OCS dose at Week 28

4.2.5.1 Definition

The percent reduction from baseline in the daily OCS dose at Week 28 whilst maintenance asthma control is categorised into binary groups depending whether a reduction from baseline in final daily OCS dose at Week 28 for a participant is $\geq 50\%$ or not.

4.2.5.2 Derivation

The derivation of percent change from baseline in daily maintenance OCS dose, baseline and final daily OCS dose is presented in Section 4.2.1.2.

For each treatment group, the number of participants having at least 50% reduction in final daily OCS dose is calculated. The proportion of such participants is calculated for each treatment group as:

Number of participants with $\geq 50\%$ reduction / number of participants in treatment group

4.2.5.3 Handling of Dropouts and Missing Data

The same approach of handling dropouts and missing data applies as for primary endpoint (Section 4.2.1.3).

4.2.5.4 Primary Analysis

The number and proportion of participants with $\geq 50\%$ reduction from baseline in final daily OCS at Week 28 is presented.

The proportion of participants with $\geq 50\%$ reduction from baseline in final daily OCS at Week 28 is analysed using a logistic regression model as described for the proportion of participants with 100% reduction in OCS in Section 4.2.3.4. The response variable in the model is the binary status showing whether a reduction from baseline in final daily OCS dose at Week 28 for a participant is $\geq 50\%$ (status=1) or not (status=0).

4.2.6 Secondary endpoint - Annualised asthma exacerbation rate (AAER) over 28 weeks

4.2.6.1 Definition

To support the secondary objective assessing the ability of tezepelumab 210 mg to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction, the AAER over 28 weeks is calculated.

An asthma exacerbation (recorded on the exacerbation eCRF page) is defined in the CSP Section 8.1.2 as a worsening of asthma that leads to any of the following:

- A temporary bolus/burst of systemic corticosteroids or a temporary increase in stable OCS background dose for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids is considered equivalent to a 3-day bolus/burst of systemic corticosteroids.

Note: Per protocol up titration of maintenance OCS dose to 1 level higher (as described in the CSP Table 10) is not considered an exacerbation event.

- An ER or urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above).

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

The start of an exacerbation is defined in the CSP as the start date of additional systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER/UC visits requiring additional systemic corticosteroids, or date of hospital admissions due to asthma, whichever occurs earlier. The end date of an exacerbation is defined in CSP as the last day of additional systemic corticosteroids or of a temporary increase in a stable OCS background dose, date of ER/UC/hospital discharge, whichever occurs later.

4.2.6.2 Derivation

Data collected after initiation of therapy with another biologic for treatment of asthma are:

- set to missing for the purpose of AAER (in years) derivation,
- imputed assuming an unfavourable outcome for the purpose of statistical model.

The AAER (in years) over 28 weeks in each treatment arm is calculated as the total number of asthma exacerbations over 28 weeks in a treatment arm divided by the total time at risk over 28 weeks in that arm. The time at risk (years) over 28 weeks is derived as follows:

Step 1: follow-up time, including time of exacerbations is calculated as follows:

- If a participant attended Week 28 visit: [earliest (date of visit at Week 28, date of last exacerbation assessment status from the EXACD eCRF form, date of initiation of another biologic for asthma reason) – date of randomisation + 1] / 365.25. The date of visit at Week 28 is used irrespective of how late this may have occurred in relation to the protocol schedule.
- If Week 28 visit is missing for a participant: [earliest {date of randomisation + 196 days + 5 days; date of initiation of another biologic for asthma reason, latest(date of last available visit including IPD visit, date of death, date of last exacerbation assessment status from the EXACD eCRF form)} – date of randomisation + 1] / 365.25

Step 2: time at risk, excluding time of exacerbations is calculated as follows:

The time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur divided by 365.25, is subtracted from the follow-up time calculated in Step 1.

Additional systemic corticosteroid treatments, ER or UC visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation is not regarded as a new exacerbation. To be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled. If the end date of the first

exacerbation and the start date of the second exacerbation are less than 7 days apart, then these are counted as one exacerbation.

It should be noted that the date of last assessment of exacerbation status from the eCRF might be later than the last available visit during the planned treatment period, in the case that the participant remained in the study with incomplete follow-up options after early discontinuation of study intervention.

The exacerbations that occur after a participant has discontinued study intervention but before the end of the time at risk are still accounted when deriving the total number of exacerbations.

Any exacerbation that starts within the time at risk, calculated as in Step 1, but ends after this time point is included in analyses, with the end date adjusted to be no later than the time at risk. Any exacerbation that starts after the time at risk, calculated as in Step 1, is not included in analyses.

4.2.6.3 Handling of Dropouts and Missing Data

The examples of missing data are provided in Section 4.2.1.3. For the purpose of statistical analysis post intercurrent event of initiation of another biologic for treatment of asthma is imputed assuming an unfavourable outcome.

4.2.6.4 Primary Analysis

Number and percentages of participants with at least one exacerbation as well as with specific number of exacerbations (0, 1, etc.) is presented. The number of exacerbations per participant as well as total days of exacerbations and total days of exacerbations per participant is presented. The total number of exacerbations, total time at risk (years) and AAER estimated as defined in Section 4.2.6.2 are presented.

AAER in the tezepelumab group is compared to that seen in the placebo group using a negative binomial model. The response variable in the model is the number of asthma exacerbations experienced by a participant over the 28-week planned treatment. Treatment, region and history of exacerbations (≤ 2 or > 2 in previous 24 months) is included as factors, and log baseline blood eosinophil counts are included as a continuous covariate in the model. The logarithm of the time at risk (in years) for exacerbation in the study is used as an offset variable in the model, to adjust for participants having different follow-up times during which the events occur. The model is used to estimate the rate ratio and its 95% confidence interval.

Adjusted (model-based) exacerbation rates are presented using the marginal rates approach described in Bartlett 2018.

4.2.6.5 Additional Analyses

Rate of asthma exacerbation associated with ER/UC visit or hospitalisation over 28 weeks

To assess the effect of tezepelumab on other endpoints associated with asthma exacerbations, an annualised rate of exacerbations associated with emergency room/urgent care visit or hospitalisation is chosen as a supportive endpoint (a subset of the endpoint defined in Section 4.2.6.1, specifically the 2nd and 3rd bullets only).

The derivation details for this endpoint are similar to those in Section 4.2.6.2.

Annualised rates for exacerbations due to ER/UC visits or hospitalisations are summarised descriptively and analysed using a similar model as for the primary analysis described in Section 4.2.6.4.

Rate of asthma exacerbation associated with ER/UC visit or hospitalization (adjudicated) over 28 weeks

The Independent Adjudication Committee assesses whether cases of ER/UC and hospitalizations are due to a worsening of asthma.

The exacerbations associated with hospitalisations and ER/UC visits that are adjudicated not to be asthma related are removed from the analysis, and in which hospitalisations and ER visits that are adjudicated to be asthma related are added. The derivation details for this endpoint are similar to those in Section 4.2.6.2. Any events which are adjudicated with an “undetermined” outcome is categorised as asthma related when the investigator has judged the event as an asthma exacerbation, and as non-asthma related when the investigator has judged the event not to be an asthma exacerbation.

Annualised exacerbation rates which consider adjudicated outcomes are analysed with descriptive statistics. In addition, analogous analysis is performed for exacerbations due to ER visits or hospitalisations.

Proportion of participants who did not experience an asthma exacerbation over 28 weeks

The proportion of participants who did not experience an asthma exacerbation during the 28-week planned treatment period is also analysed. A participant is considered to have completed the planned treatment period, if the planned treatment period is greater than 191 days (Day 196 minus 5, to account for visit windowing).

Participants who had no asthma exacerbations during the planned treatment period and who completed the planned treatment period (to Week 28) without initiating another biologic for asthma reason are defined as exacerbation free/successful outcome [a].

Participants who did not complete the planned treatment period or who initiated another biologic for asthma reason during the planned treatment period are defined as not having a successful outcome for this endpoint [b] [c].

Participants who completed the planned treatment period without initiating another biologic for asthma reason and had an asthma exacerbation are defined as not having a successful outcome for this endpoint [d].

	No exacerbation	Exacerbation
Completed planned treatment period without initiating another biologic for asthma reason	[a] Exacerbation free/successful outcome	[d] No successful outcome
Did not complete treatment period or initiate another biologic for asthma reason during the planned treatment period	[b] No successful outcome	[c] No successful outcome

The proportion of participants who did not experience an asthma exacerbation during the 28-week planned treatment period is calculated for each treatment group as:

Number of participant's exacerbation free [a] / number of participants in treatment group.

The proportion of participants who had no asthma exacerbation during the planned treatment period is summarised descriptively and analysed using a logistic regression model. An odds ratio and 95% confidence interval are estimated from the logistic regression model which includes factors for treatment, region, history of exacerbations (≤ 2 or > 2 in previous 24 months) and logarithm of baseline blood eosinophil counts.

4.2.6.6 Subgroup Analyses of Secondary Endpoint

To explore the treatment effect on annualized exacerbation rate over 28 weeks across biomarker (EOS, FeNO, IgE) subgroups defined in Section 3.3.1.6, a similar approach of handling intercurrent events is applied and similar model is fitted as for the analysis of described in Section 4.2.6.4 with additional factors for the relevant subgroup variable and its interaction with treatment. The estimate of the treatment effect and its 95% CI within each of the subgroup categories is presented. A p-value for the treatment by subgroup interaction is not presented for each of these models. If any of the subgroups have fewer than 10 participants in one or both treatment groups, this subgroup level is not included in the model. If that leaves only one subgroup level, the model is not fitted for that categorical variable.

4.2.7 Secondary Endpoint - Time to first asthma exacerbation

4.2.7.1 Definition

To support the secondary objective assessing the ability of tezepelumab 210 mg to prevent asthma exacerbations in adult participants with OCS-dependent asthma while OCS dose reduction, time to first exacerbation is presented. Exacerbation is defined in Section 4.2.6.1.

4.2.7.2 Derivation

Time (in days) from randomisation to the first asthma exacerbation is calculated as follows:

Time to 1st exacerbation (days) = (Start date of 1st exacerbation – date of randomisation) + 1.

Participants without an exacerbation over 28 weeks or prior to initiation of another biologics are censored on the date defined as earliest(date of initiation of another biologic for asthma reason, latest(last exacerbation assessment status from the EXACD eCRF form, date of death).

4.2.7.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis.

4.2.7.4 Primary Analysis

Time to first asthma exacerbation is summarised using Kaplan-Meier plot, and analysed using a Cox proportional hazards model with factors of treatment, region and history of exacerbations (≤ 2 or > 2 in previous 24 months) and with continuous covariate of logarithm of baseline blood eosinophil counts.

4.2.8 Secondary Endpoint - Change from baseline in Asthma Control Questionnaire 6 (ACQ-6) score at Week 28

4.2.8.1 Definition

The ACQ-6 questionnaire includes questions on:

- Awakening at night by symptoms
- Limitations of normal daily activities
- Waking in the morning with symptoms
- Dyspnoea
- Wheeze
- Daily rescue medication

The questions of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The endpoint is the change from baseline in unweighted mean of ACQ-6 score at Week 28.

4.2.8.2 Derivation

Data collected after initiation of therapy with another biologic for treatment of asthma are:

- set to missing for the purpose of descriptive summary
- imputed assuming an unfavourable outcome for the purpose of statistical model.

The ACQ-6 score is computed as the unweighted mean of the responses to the 6 questions presented in Section 4.2.8.1. If response to any of the questions is missing, the ACQ-6 score is set to missing.

The derivation of a change from baseline in ACQ-6 score for each individual item at any post-baseline time point is described in Section 3.3.1.3. Baseline ACQ-6 score and each individual item scores are defined as in Section 3.3.1.1.

4.2.8.3 Handling of Dropouts and Missing Data

The examples of missing data are provided in Section 4.2.1.3. For the purpose of statistical analysis post intercurrent event of initiation of another biologic for treatment of asthma or death is imputed assuming an unfavourable outcome (for details see Section 4.2.2.4). Other missing data is imputed assuming MAR.

4.2.8.4 Primary Analysis

The absolute values and changes from baseline in unweighted mean ACQ-6 score and individual items are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

The same statistical analysis as for change from baseline in pre-BD FEV₁, described in Section 4.2.2.4, is applied for the change from baseline in ACQ-6 score as well for each individual item. The corresponding baseline ACQ-6 score (total or for individual item) is used as covariate instead of baseline pre-BD FEV₁. The results are presented as shown in Section 4.2.2.4.

4.2.8.5 Additional Analyses

Other endpoints based on ACQ-6 to be reported at each time point include:

- ACQ-6 responder (Yes=1/No=0):
 - Responder: change from baseline ACQ-6 score ≤ -0.5 ,
 - Non-Responder: change from baseline ACQ-6 score > -0.5 .
- ACQ-6 response (Improved/No Change/Deterioration):
 - Improvement: change from baseline ACQ-6 score ≤ -0.5 ,
 - No Change: $-0.5 < \text{change from baseline ACQ-6 score} < 0.5$,
 - Deterioration: change from baseline ACQ-6 score ≥ 0.5 .
- Participant asthma control as measured by ACQ-6 score:

- Well controlled: ACQ-6 score ≤ 0.75 ,
- Partly controlled: $0.75 < \text{ACQ-6 score} < 1.5$,
- Uncontrolled: ACQ-6 score ≥ 1.5 .

If baseline and/or any post-baseline value is missing at any time point, then the change from baseline at the time point is set to missing. A participant with missing post-baseline value or missing change from baseline at a time point, is classified to “unknown” category at the time point.

The number and proportion of ACQ-6 responder (responders/non-responders/unknown), ACQ-6 response (improved, no change, deterioration, unknown) and asthma control status based on ACQ-6 (well controlled, partly controlled, uncontrolled, unknown) are presented over time. Additionally, the percentage of ACQ-6 responders is displayed graphically over time by treatment arm.

In addition, the ACQ-6 responder status (responder/non-responder) at Week 28 is analysed using the logistic regression model. The ACQ-6 scores, imputed as described in Section 4.2.8.4, are classified into responder/non-responder and used in the model as the response variable. The response variable in the model is the binary responder status at Week 28. Treatment and region are included as factors in this model. Baseline ACQ-6 score and log baseline blood eosinophil counts are included in the model as a continuous linear covariate. An odds ratio and 95% confidence interval estimated from the model are presented.

4.2.9 Secondary Endpoint – Weekly mean home peak expiratory flow (PEF) (morning and evening) at Week 28

4.2.9.1 Definition

Home PEF testing is performed by a participant in the morning upon awakening (and prior to taking their AM asthma controller) and in the evening at bedtime (and prior to taking their PM asthma controller). Participants should perform 3 successive peak flow manoeuvres while sitting or standing, but in the same position at every testing. The best (highest) morning and evening PEF is used from the available individual PEF measurements on each day in the morning and evening respectively.

4.2.9.2 Derivation

Data collected after initiation of therapy with another biologic for treatment of asthma are:

- set to missing for the purpose of descriptive summary
- imputed assuming an unfavourable outcome for the purpose of statistical model.

Weekly mean home-based PEF at baseline is defined in Section 3.3.1.1. Weekly means at any post-baseline time point is derived as presented in Section 3.3.2. If a participant is missing one of the daily measurements (evening or morning), then the whole day is

missing. The changes from baseline are defined in Section 3.3.1.3 and calculated separately for morning and evening peak expiratory flow (PEF).

4.2.9.3 Handling of Dropouts and Missing Data

The examples of missing data are provided in Section 4.2.1.3. For the purpose of statistical analysis post intercurrent event of initiation of another biologic for treatment of asthma is imputed assuming an unfavourable outcome. Other missing data is imputed assuming MAR.

4.2.9.4 Primary Analysis

The absolute values and changes from baseline in the weekly mean home morning and evening PEF are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

The same statistical analysis as for change from baseline in pre-BD FEV₁, described in Section 4.2.2.4, is applied for the change from baseline in the weekly mean home morning and evening PEF. The corresponding baseline PEF value (morning and evening) is used as covariate instead of baseline pre-BD FEV₁. Each of the 28 weeks used for weekly mean calculation replaces visit in the model. The results are presented as shown in Section 4.2.2.4.

4.2.10 Secondary Endpoint - Change from baseline in AQLQ(S)+12 total score

4.2.10.1 Definition

In the AQLQ(S)+12 the participants are asked to recall their experiences during the previous 2 weeks and to answer each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment).

There are 4 domains covered by the questionnaire assessing:

- symptoms,
- activity limitations,
- emotional function,
- environmental stimuli.

The endpoint is the change from baseline in AQLQ(S)+12 total score at Week 28. The change from baseline in each domain is also calculated.

4.2.10.2 Derivation

Data collected after initiation of therapy with another biologic for treatment of asthma are:

- set to missing for the purpose of descriptive summary

- imputed assuming an unfavourable outcome for the purpose of statistical model.

The AQLQ(S)+12 total score is calculated as the mean response to all questions. The 4 individual domain scores are the means of the responses to the questions in each of the domains. Higher scores indicate better outcomes. The following are the question numbers on the AQLQ(S)+12 questionnaire relating to each domain:

Table 9 AQLQ(S)+12 domains

Domain	AQLQ(S)+12 question number
Symptoms	6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitations	1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function	7, 13, 15, 21, 27
Environmental Stimuli	9, 17, 23, 26

If response to any of the questions is missing, the AQLQ(S)+12 total score is set to missing. If response to a question within a domain is missing, the score for that domain is set to missing.

The derivation of a change from baseline in AQLQ(S)+12 total score and in each domain at any post-baseline time point is presented in Section 3.3.1.3. Baseline AQLQ(S)+12 score and each domain scores are derived as in Section 3.3.1.1. The results are presented as shown in Section 4.2.2.4.

4.2.10.3 Handling of Dropouts and Missing Data

The examples of missing data are provided in Section 4.2.1.3. For the purpose of statistical analysis post intercurrent event of initiation of another biologic for treatment of asthma is imputed assuming an unfavourable outcome. Other missing data is imputed assuming MAR.

4.2.10.4 Primary Analysis

The absolute value and changes from baseline in AQLQ(S)+12 total score and in domains are summarised descriptively (n, mean, SD, median, minimum and maximum) over time using observed data.

The same statistical analysis as for change from baseline in pre-BD FEV₁, described in Section 4.2.2.4, is applied for the change from baseline in AQLQ(S)+12 total score as well in each domain. The corresponding baseline AQLQ(S)+12 score (total or for a domain) is used as covariate instead of baseline pre-BD FEV₁. The results are presented as shown in Section 4.2.2.4.

4.2.10.5 Additional Analyses

Other variables based on AQLQ(S)+12 to be reported at each time point include:

- AQLQ(S)+12 responder (Yes=1/No=0):
 - Responder: Change from baseline AQLQ(S)+12 total score ≥ 0.5
 - Non-responder: Change from baseline AQLQ(S)+12 total score < 0.5
- AQLQ(S)+12 response (Improved/No Change/Deterioration):
 - Improvement: Change from baseline AQLQ(S)+12 total score ≥ 0.5
 - No change: $-0.5 < \text{Change from baseline AQLQ(S)+12 total score} < 0.5$
 - Deterioration: Change from baseline AQLQ(S)+12 total score ≤ -0.5 .

If baseline and/or any post-baseline value is missing at any time point, then the change from baseline at the time point is set to missing. A participant with missing post-baseline value or missing change from baseline at a time point, is classified to “unknown” category at the time point.

The number and proportion of AQLQ(S)+12 responder (responders/non-responders/unknown) and AQLQ(S)+12 response (improved, no change, deterioration, unknown) are presented over time. Additionally, the percentage of AQLQ(S)+12 responders is displayed graphically over time by treatment arm.

In addition, the AQLQ(S)+12 responder status at Week 28 is analysed in similar way as ACQ-6 responder status described in Section 4.2.8.5. Baseline AQLQ(S)+12 total score is included in the model, instead of the baseline ACQ-6 score, as a continuous linear covariate.

4.2.11 Secondary Endpoint - Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score

4.2.11.1 Definition

The SGRQ is a 50-item PRO instrument developed to measure the health status of participants with airway obstruction diseases. The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (Symptoms, Activity and Impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment.

The endpoint is the change from baseline in SGRQ total score at Week 28. The change from baseline in each domain is also calculated.

4.2.11.2 Derivation

Data collected after initiation of therapy with another biologic for treatment of asthma are:

- set to missing for the purpose of descriptive summary
- imputed assuming an unfavourable outcome for the purpose of statistical model.

The SGRQ scores are calculated according to the SGRQ manual (version 2009). The derivation of a change from baseline in SGRQ total score and in each domain at any post-baseline time point is presented in Section 3.3.1.3. Baseline SGRQ score and each domain scores are derived as in Section 3.3.1.1.

4.2.11.3 Handling of Dropouts and Missing Data

The examples of missing data are provided in Section 4.2.1.3. For the purpose of statistical analysis post intercurrent event of initiation of another biologic for treatment of asthma is imputed assuming an unfavourable outcome. Other missing data is imputed assuming MAR.

4.2.11.4 Primary Analysis

The absolute values and change from baseline in SGRQ total score and in domains are summarised descriptively (n, mean, SD, median, minimum and maximum) over time using observed data.

The change from baseline in SGRQ total scores is analysed using an analysis of covariance model (ANCOVA). Treatment and region are included as categorical covariates, and baseline SGRQ score and log baseline blood eosinophil counts are included as continuous covariates in the model. The adjusted mean changes from baseline for each treatment arm together with its 95% confidence interval is presented from the model, as well as the mean difference with 95% confidence interval (CI).

Similar models are applied for each SGRQ domain separately. Baseline SGRQ score is replaced by baseline SGRQ score of appropriate domain score.

4.2.11.5 Additional Analyses

Other variables based on SGRQ to be reported at each time point include:

- SGRQ responder (Yes=1/No=0):
 - Responder: change from baseline in SGRQ total score ≤ -4
 - Non-responder: change from baseline in SGRQ total score > -4
- SGRQ deterioration (Yes=1/No=0):
 - deterioration: change from baseline in SGRQ total score ≥ 4
 - Lack of deterioration: change from baseline in SGRQ total score < 4

Data collected after the initiation of another biologic for treatment of asthma is set to missing. If baseline and/or any post-baseline value is missing at any time point, then the change from baseline at the time point is set to missing. A participant with missing post-

baseline value or missing change from baseline at a time point, is classified to “unknown” category at the time point.

The number and proportion of SGRQ responder (responders/non-responders/unknown) and SGRQ deterioration (yes/no/unknown) are presented over time.

In addition, SGRQ responder status at Week 28 is analysed in similar way as ACQ-6 responder status described in Section 4.2.8.5. Baseline SGRQ total score is included in the model, instead of the baseline ACQ-6 score, as a continuous linear covariate.

4.2.12 Secondary Endpoint - Change from baseline in biomarkers

4.2.12.1 Definition

The effect of tezepelumab on biomarkers is measured by the change from baseline at each post-baseline time point in:

- Fractional exhaled nitric oxide (ppb)
- Peripheral blood eosinophils ($10^9/L$ and cells/ μL)
- Total serum IgE (mg/L and IU/mL).

The definition of baseline is given in Section 3.3.1.1.

Note that absolute eosinophil counts are delivered by both CCI and CCI laboratory. The latter ones are used in the statistical analyses.

Analyses for any additional exploratory biomarkers may be described in a separate exploratory analysis plan. These results will be reported outside the main CSR, in an addendum, or separately in a scientific report or publication.

4.2.12.2 Derivation

Data collected after initiation of therapy with another biologic for treatment of asthma is set to missing.

The derivation of a change from baseline in biomarker (EOS, FeNO, IgE) levels at any post-baseline time point is presented in Section 3.3.1.3. Baseline values are defined as in Section 3.3.1.1.

4.2.12.3 Handling of Dropouts and Missing Data

No imputation is applied for the analysis of biomarkers data.

4.2.12.4 Primary Analysis

The change from baseline in biomarker (EOS, FeNO, IgE) levels are summarised descriptively (n, mean, SD, median, minimum and maximum) over time. IgE is summarized using both absolute and log-transformed values, all other analyses are based on log-transformed values only.

Change from baseline in biomarker levels in the tezepelumab group is compared to that seen in the placebo group using a model for repeated measures. This model is used to estimate the treatment effect at Week 28 and its 95% confidence interval. The response variable in the model is the change from baseline at each scheduled post randomisation visit up to and including Week 28. Treatment, visit, region and treatment by visit interaction will be included as factors in this model. Baseline biomarker level is included in the model as a continuous linear covariate. Baseline by visit interaction is not included as a covariate in the model.

Unstructured covariance is assumed to model the relationship between pairs of response variables taken at different visits on the same subject. If the model fails to converge with unstructured covariance, the Compound Symmetry is applied.

Note that eosinophil ($10^9/L$) and total serum IgE (mg/L) data are also included in the summaries of laboratory data.

4.2.13 Exploratory endpoint - Change from baseline in pre- and post-BD lung function measures

4.2.13.1 Definition

The effect of tezepelumab compared with placebo on other pre-BD and post-BD lung function measures is explored. Including, but not limited to, the change from baseline in:

- pre- and post-BD forced vital capacity (FVC),
- pre- and post-BD forced expiratory flow over 25-75% of the vital capacity (FEF_{25-75%}),
- post-BD forced expiratory volume in 1 second (FEV₁).

4.2.13.2 Derivation

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The derivation of a change from baseline in pre- and post-BD lung function measures at any post-baseline time point is described in Section 3.3.1.3. Baseline value is defined as in Section 3.3.1.1.

4.2.13.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.13.4 Primary Analysis

The absolute changes from baseline in each pre- and post-BD lung function measures are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

4.2.14 Exploratory endpoint - Change from baseline in EQ-5D-5L score

4.2.14.1 Definition

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, and 5 = extreme problems) that reflect increasing levels of difficulty.

The participant is asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale (VAS), where the participant is asked to rate current health status on a scale of 0 - 100, with 0 being the worst imaginable health state.

4.2.14.2 Derivation

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The health state valuation (an index-based value) for the EQ-5D-5L is derived from the 5 dimensions defined in Section 4.2.14.1 using the UK population-based preference weights. Further details are given in van Hout et al 2012 and Devlin et al 2017.

The derivation of a change from baseline in VAS and health state valuation index at any post-baseline time point is presented in Section 3.3.1.3. Baseline values of VAS, health state valuation index and 5 dimensions are derived as in Section 3.3.1.1.

4.2.14.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.14.4 Primary Analysis

Number and percentage of participants in each response option is presented for each EQ-5D-5L dimension over time. The change from baseline in EQ-5D-5L VAS and health state valuation index are summarised descriptively (n, mean, SD, median, minimum and maximum) over time. Data collected after initiation of another biologic is excluded from analyses.

4.2.15 Exploratory endpoint - Change from baseline in weekly mean daily Asthma Symptom Diary score

4.2.15.1 Definition

Asthma symptoms during night-time and daytime are recorded by the participant each morning and evening in the Asthma Symptom Diary (ASD). Symptoms are recorded using a scale from 0 to 4, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning), and total (daily) score are calculated separately.

4.2.15.2 Derivation

It is expected that participants complete the ASD once in the evening and once in the morning. If multiple evening measurements and/or multiple morning measurements are recorded on a particular day, then the first evening and/or first morning measurement respectively is used for all derivations required for analysis.

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The total (daily) ASD score is calculated by taking the mean of the 10 component items recorded in the evening and the following morning. The daytime ASD score is defined as the mean of 5 items recorded in the evening, and the night-time ASD score is the mean of 5 items recorded the following morning. If one or more of the 5 items for either night-time or daytime asthma symptom score is missing on a given day (evening followed by morning), then the total (daily) ASD score for that day is set to missing. If all 5 items are present, then the daytime/night-time ASD score (as applicable) is calculated.

Weekly mean scores and changes from baseline in daytime, night-time, total (daily) scores and individual items is calculated. Weekly mean scores for baseline are defined in [Section 3.3.1.1](#).

Individual symptom scores within the ASD are derived as follows:

- Severity of wheezing: mean of combined daytime and night-time items. If either the daytime or night-time item is missing, then severity of wheezing is missing.
- Shortness of breath: mean of combined daytime and night-time items. If either the daytime or night-time item is missing, then shortness of breath is missing.
- Severity of cough: mean of combined daytime and night-time items. If either the daytime or night-time item is missing, then severity of cough is missing.
- Severity of chest tightness: mean of combined daytime and night-time items. If either the daytime or night-time item is missing, then severity of chest tightness is missing.
- Frequency of waking (night-time item).
- Limit activities (daytime item).

The derivation of a change from baseline at any post-baseline week is described in [Section 3.3.1.3](#).

4.2.15.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.15.4 Primary Analysis

The absolute values and changes from baseline in weekly means of ASD daytime, night-time, total (daily) scores and individual items are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

4.2.15.5 Additional Analyses

Other endpoint based on total (daily) Asthma Symptom Diary score to be reported at each time point is ASD responder (Yes=1/No=0):

- Responder: Change from baseline in weekly mean ASD score ≤ -0.5
- Non-responder: Change from baseline in weekly mean ASD score > -0.5 .

If baseline and/or any post-baseline value is missing at any time point, then the change from baseline at the time point is set to missing. A participant with missing post-baseline value or missing change from baseline at a time point, is classified to “unknown” category at the time point.

The number and proportion of ASD responder (responders/non-responders/unknown) is presented over time. The percentage of ASD responders is displayed graphically over time.

Other endpoint related to ASD scores is asthma symptomatic days. The number of asthma symptomatic days for a participant is calculated as the number of days for which the ASD score (i.e., mean of 10 items) ≥ 1 within a week (as described in Section 3.3.2). The change from baseline in the percentage of symptomatic days (out of the number of available days within the week) is calculated at each post-baseline week.

The percentage of asthma symptomatic days (absolute values and changes from baseline) are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

4.2.16 Exploratory endpoint - Number of asthma specific resource utilisations

4.2.16.1 Definition

Health care resource utilisation due to asthma is recorded on the eCRF, including:

- Ambulance transport
- Hospitalization
 - Intensive care (days in intensive care)
 - General care (days in general care)
- Emergency room visit
- Hospital admission or emergency department > 24 hours
- Visit to specialist
- Visit to primary health care physician
- Other health care visit
- Home visit, physician
- Home visit, other health care
- Telephone call, physician
- Telephone call, nurse
- Telephone call, other physician/health care provider

- Spirometry
- Advanced pulmonary function test
- Plain chest X-ray
- Computer tomography
- Oxygen initiated

4.2.16.2 Derivation

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The number of times (or days, as appropriate) for each item described in Section 4.2.16.1 is calculated at baseline, up to Week 28, and up to Week 40.

The number of times (or days) up to Week 28 (or up to Week 40) per participant is determined as:

Sum of 'total number of times (or days)' as entered on the eCRF page from baseline up to Week 28 (or up to Week 40).

4.2.16.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.16.4 Primary Analysis

All HRU items defined in Section 4.2.16.1 are summarised descriptively (n, mean, SD, median, minimum and maximum value) at baseline, up to Week 28, and up to Week 40.

4.2.17 Exploratory endpoint - Pharmacodynamic Endpoints

4.2.17.1 Definitions

Pharmacodynamics parameters include but not limited to serum biomarkers (TSLP, IL-5 and IL-13).

4.2.17.2 Derivations

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The derivation of a change from baseline in serum biomarker levels at any post-baseline time point is presented in Section 3.3.1.3. Baseline values are defined as in Section 3.3.1.1.

4.2.17.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the endpoint.

4.2.17.4 Primary Analysis

The change from baseline in serum biomarkers levels are summarised descriptively (n, mean, SD, median, minimum and maximum) and presented graphically over time.

4.2.18 Exploratory endpoint - Transcriptomic and Genomics/genetics profiling

Transcriptomic and pharmacogenomic biomarkers are reported separately from the CSR and are outside the scope of this SAP.

4.2.19 Exploratory endpoint - Mean daily exposure of systemic corticosteroids (mg/day) taken for asthma reasons over 28 weeks.

4.2.19.1 Definitions

The mean daily exposure of systemic corticosteroids (SCS) (mg/day) taken for asthma reasons over the 28 weeks. The endpoint allows for an assessment of the overall load of SCS for asthma reasons during the planned treatment period, in addition to maintenance OCS.

4.2.19.2 Derivations

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The endpoint is calculated using SCS medications collected on the ECSYSCRT eCRF page except SCS with a therapy reason of “Non-asthma condition” and “Other”. All SCS are converted to a prednisone equivalent dose as described in CSP Appendix G.

The endpoint is calculated according the following formula:

The mean daily exposure of SCS (mg/day) over 28 weeks = Cumulative SCS dose over the 28 weeks / minimum(total number of days in the 28-week planned treatment period, total number of days from the randomisation visit until initiation of another biologic for asthma reason).

where:

Cumulative SCS dose over the 28 weeks = sum of daily SCS dose over the 28 weeks of planned treatment period or earlier if another biologic for asthma reason is initiated.

4.2.19.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the endpoint.

4.2.19.4 Primary Analysis

The mean daily exposure of SCS (mg/day) over 28 weeks is summarised descriptively (n, mean, SD, median, minimum and maximum value). In addition, the mean value (± 1 SE) of the cumulative SCS dose (mg) over 28 weeks is displayed graphically over time (days).

4.2.19.5 Additional Analyses

Systemic corticosteroids (SCS) taken for non-asthma reasons

SCS for non-asthma reasons is identified as medications recorded in the eCRF page with a therapy reason of “Non-asthma condition” and “Other”. The number and percentage of

participants using SCS for non-asthma reasons during the planned treatment period is summarised by treatment group. Moreover, the number and percentage are provided for subgroups of participants taking oral or non-oral systemic corticosteroids for reasons other than asthma during the planned treatment.

In addition, the total number of days of systemic corticosteroid use for non-asthma reasons per participant during the planned treatment period is also summarised.

4.2.20 Other Endpoints - Global asthma symptom score

4.2.20.1 Definition

The total daily global asthma symptom score is derived from a single item global assessment of asthma symptoms each morning and evening. This is not the same as the total score derived from the ASD.

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

4.2.20.2 Derivation

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The total daily asthma symptom score is calculated by taking the sum of the daytime score recorded in the evening and the night-time score recorded the following morning. If a participant is missing a value for either night-time or daytime asthma symptom score on a given day (evening followed by morning), then the total score for that day is set to missing.

For weekly mean scores baseline is defined in Section 3.3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 4.2.15.2. The derivation of a change from baseline at any post-baseline time point is presented in Section 3.3.1.3.

4.2.20.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.20.4 Primary Analysis

The absolute values and changes from baseline in the weekly mean daytime, night-time and daily global asthma symptom total score are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

4.2.21 Other Endpoints - Rescue medication use

4.2.21.1 Definition

The number of rescue medication inhalations (puffs) and nebuliser treatments taken is recorded by the participant in the diary twice daily (i.e., in the morning and evening) beginning the evening of Visit 1 until the morning of Visit 13.

Daytime use of medications is defined as the number of inhalations/nebuliser treatments taken between the morning and evening lung function assessments that is recorded in the evening. Night-time use of medications is defined as the number of inhalations/nebuliser treatments taken between the evening and the morning that is recorded in the morning. Inhaler usage is reported as the number of puffs in a given period whereas nebulizer use is reported as the number of times.

4.2.21.2 Derivation

Data collected after initiation of another biologic for treatment of asthma is set to missing.

The number of inhalations of rescue medication and nebulizer treatments captured in the daily diary each day is calculated per participant. If a participant is missing a value for either night-time or daytime rescue medication on a given day (evening followed by morning), then the total rescue medication use for that day is set to missing.

The daily rescue medication use is calculated as follows:

Number of night inhaler puffs + 2 x [number of night nebulizer times] + number of day inhaler puffs + 2 x [number of day nebulizer times].

For weekly mean scores baseline is defined in Section 3.3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 4.2.15.2. The derivation of a change from baseline at any post-baseline time point is presented in Section 3.3.1.3.

4.2.21.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.21.4 Primary Analysis

The absolute values and changes from baseline in the weekly mean rescue medication use are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

4.2.22 Other Endpoints - Night-time awakenings requiring rescue medication

4.2.22.1 Definition

Night-time awakenings due to asthma symptoms are recorded by the participant in the diary each morning, beginning in the morning after Visit 1 until the morning of Visit 13, by

answering the question whether he/she woke up during the night due to asthma symptoms and was required to take rescue medication with a “yes” or “no” response.

Only night-time awakenings that required rescue medication are included in the analysis.

4.2.22.2 Derivation

Data collected after initiation of another biologic for treatment of asthma is set to missing. Weekly mean of the in the percentage of available nights within the week for which there was an awakening due to asthma that required rescue medication for baseline is defined in Section 3.3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 4.2.15.2.

Change from baseline in the percentage of available nights within the week for which there was an awakening due to asthma that required rescue medication is calculated at each post-baseline week as described in Section 3.3.1.3.

4.2.22.3 Handling of Dropouts and Missing Data

There is no imputation of missing data in the analysis of the exploratory endpoint.

4.2.22.4 Primary Analysis of Other Endpoint

The absolute values and changes from baseline in the weekly mean number of night-time awakenings due to asthma and requiring rescue medication are summarised descriptively (n, mean, SD, median, minimum and maximum) over time.

4.3 Pharmacokinetics

The third-party vendor analysing the PK samples are unblinded to the randomised treatment assignments of all participants; no one from the study team has access to the PK data until after the study has been unblinded. The assay for determination of tezepelumab concentrations is only performed using samples for participants randomised to tezepelumab. Participants who are randomised to placebo do not have their PK samples analysed by the vendor laboratory.

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

All analyses of PK variables are based on the PK analysis set as defined in Section 4.1.2.1.

Serum tezepelumab concentrations are summarised over time 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, 28 and at the premature study intervention discontinuation visit, where appropriate. Data is assigned to weeks based on the windows defined in Section 3.3.2.

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

- Only pre-dose samples at week 0.
- Only pre-dose samples at week 12 that were also between ≥ 21 and ≤ 35 days post the previous dose.
- Only samples that were taken between ≥ 21 and ≤ 35 days post the previous dose for week 28.

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 are 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 are reported as not calculable (NC)
- If all the concentrations are NQ, the geometric mean and arithmetic mean are reported as NQ and the CV and SD as NC
- The median, minimum and maximum are also reported.

The LLOQ of tezepelumab in serum is 0.010 µg/mL.

If appropriate, descriptive statistics of tezepelumab concentrations over time are also presented by ADA category (treatment-emergent ADA positive, non-treatment-emergent ADA positive and ADA negative, where treatment emergent for ADA is defined below in Section 4.4).

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

4.4 Immunogenicity

Serum samples for determination of the presence of anti-drug antibodies (ADA) and neutralising antibodies (nAb) are collected at baseline and at Week 12 prior to study intervention administration, at Week 28, Week 40 and at the premature study intervention discontinuation visit, where appropriate.

Samples are used to detect the presence of ADA and nAb, according to validated assays performed by a designated third-party vendor. Details of the bioanalytical methods used is described in a separate bioanalytical report.

For immunogenicity, tiered analysis is performed to include screening, confirmatory, and titre of ADA assay components as well as nAb assay. Samples that are confirmed positive for ADAs is further analysed for ADA titre and the presence of nAb.

The ADA samples from all participants, regardless of treatment assignment, are analysed.

All analyses of immunogenicity variables are based on the Safety set as defined in Section [4.1.2.1](#).

The number of ADA positive participants at each visit are summarised by treatment group for the on-study period. Descriptive statistics including number of participants, median, lower and upper quartile and range of the actual ADA titres by treatment group and visit, where possible, are provided.

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

- Participants who are ADA positive at any time including baseline (ADA prevalence).
- Participants who are ADA positive at baseline only.
- Participants who are ADA positive at baseline and positive in at least one post baseline measurement.
- Participants who are ADA positive post-baseline and ADA negative at baseline (treatment induced ADA)
- Participants who are 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.
- Participants who are transiently positive; transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- Participants with treatment boosted ADA, defined as baseline positive ADA titre that was boosted to a 4 fold or higher level following study intervention administration.
- Participants with treatment emergent ADA (ADA incidence): defined as either treatment induced ADA positive or treatment boosted ADA positive.
- Participants with non treatment emergent ADA: defined as ADA positive but not fulfilling the definition of TE-ADA positive.
- Participants who are nAb positive at baseline and/or post-baseline (nAb prevalence).

- Participants who are treatment-induced nAb positive (nAb incidence)

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

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

Neutralizing ADA evaluations are conducted on confirmed ADA positive samples. The test sample is deemed positive or negative for the presence of nAb to tezepelumab relative to a pre-determined (in assay validation) statistically derived cut point. The number and proportion of participants who are nAb positive at any time are evaluated.

The evaluation of ADA impact on primary endpoint, key secondary endpoint and safety outcomes is assessed by individual listing in ADA positive participants only.

4.5 Safety Analyses

The safety analyses, including summary of exposure, adverse events, clinical laboratory and vital signs, are based on the Safety Set.

4.5.1 Exposure

4.5.1.1 Definitions and Derivations

Extent of exposure to study intervention is defined as the number of days between the date of first dose of study intervention and the date of last dose of study intervention inclusive plus the number of days allowance for the dosing interval, that is:

Extent of exposure (days) = earliest(date of last dose of study intervention + 33 days; date of death; date of study withdrawal) – date of first dose of study intervention + 1.

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

The total participant-years exposure is derived as the sum of the individual participant extent of exposure (days) for a treatment group divided by 365.25.

4.5.1.2 Presentation

Extent of exposure to study intervention is summarised descriptively (n, mean, SD, median, lower and upper quartile, minimum and maximum). The total participant-years exposure is presented.

The number of dosing occasions are also summarised.

4.5.2 Adverse Events

4.5.2.1 Definitions and Derivations

Adverse events (AEs) experienced by any participant at any time during the entire study are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version in force at the primary DBL.

Study periods AE categorization

AEs are categorised for analysis according to their onset date into the following study periods:

- AEs occurring during screening/run-in/optimization period: date of Visit 1 $\leq$ AE onset date $<$ date of first dose of study intervention,
- AEs occurring during on-treatment period: date of first dose of study intervention $\leq$ AE onset date $\leq$ earliest(date of last dose of study intervention + 33 days after the last dose of study intervention, date of death, date of study withdrawal),
- AEs occurring during post-treatment period (for participants still being followed up then): date of last dose of study intervention + 33 days $<$ AE onset date $\leq$ study completion or withdrawal date,
- AEs occurring during on-study period: date of first dose of study intervention $\leq$ AE onset date $\leq$ study completion or withdrawal date.

If the AE has a completely missing (and unresolvable) onset date, then the AE is 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 is also 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.

Adjusted incidence rate

The exposure-adjusted incidence rate (EAIR) will be calculated for each treatment as the number of participants in that treatment group reporting the AE during the analysis period divided by the total time at risk in that treatment group, where time at risk is the time to the first event for a participant who experienced the event during the analysis period and time during the analysis period for a participant who didn't experience the event. EAIR will be reported as events per 100 participant-years. EAIR will be calculated both for the on-treatment period and the on-study period (as defined in Section 3.3.1.5).

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

Adverse events of special interest

The protocol specifies Adverse Events of Special Interest (AESIs) as those which merit special attention in this study, 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 7.1.

Adjudicated adverse events

Adjudicated adverse events are specified per protocol as major adverse cardiac events (MACE), serious cardiac events, deaths and malignancies which diagnosis and causality (except for malignancy) are confirmed by the Independent Adjudication Committee.

4.5.2.2 Presentation

AEs are summarised separately for the on-treatment and on-study periods as defined in Section 3.3.1.5 unless stated otherwise. AEs occurring during the screening/run-in/optimization period, or occurring post-treatment are listed, but not summarised separately.

An overall summary table is produced showing the number and percentage of participants with at least one AE in each of the following categories: any AEs, serious adverse events (SAEs), AEs with a fatal outcome, AEs leading to discontinuation of study intervention (DAEs), any possibly related AE and any possibly related SAE. Moreover, exposure-adjusted AE summaries will be presented for the on-treatment and on-study periods respectively.

All AEs are summarised by system organ class (SOC) and preferred term (PT) assigned to the event using the MedDRA dictionary. For each PT, the number and percentage of participants reporting at least one occurrence of the event are presented (i.e. participants with multiple occurrences of the same PT are only counted once).

Similar summaries by SOC and PT are also presented for:

- Possibly related adverse events,
- SAEs,
- fatal SAEs,
- AEs leading to discontinuation of study intervention (DAEs) (on- treatment period only),
- each AESI category separately,
- Possibly related AESI,
- All AEs by PT only.

AEs are summarised by PT and maximum intensity, and by SOC, PT and causality (as determined by the investigator). If a participant reports multiple occurrences within each

PT, the maximum intensity is taken as the highest recorded (the order being mild, moderate and severe) respectively. In addition, each AESI category is summarised by causality.

Exposure-adjusted AE summaries are presented by SOC and PT for each of the following:

- All AEs,
- SAEs,
- each AESI,
- all AEs by PT only.

In these summaries, the exposure-adjusted rate are defined for each treatment as defined in Section 4.5.2.1, for all participants in that treatment group. Rates are reported as events per 100 subject-years. Additionally, risk differences between placebo and study intervention arms with their two-sided 95% CIs are presented in these summaries. For the estimation of the CIs, the Miettinen and Nurminen's score method is applied (see [Miettinen and Nurminen 1985](#)).

The number and percentage of participants with any Adverse event submitted to the IAC is summarised overall for MACE adjudication, for serious cardiac event adjudication, for malignancy adjudication and for death. In addition, the adjudicated MACE events, serious cardiac events, malignancies, and deaths are presented by SOC, PT and causality (as determined by the IAC). Exposure-adjusted AE summaries are presented as well.

4.5.3 Clinical Laboratory, Blood Sample

4.5.3.1 Definitions and Derivations

Clinical chemistry and haematology are performed by a central laboratory according to the schedule and the variable specifications described in the CSP Table 12.

In all analyses of continuous laboratory variables, any value recorded only as below Lower Limit of Quantification (LLOQ) is set to LLOQ and included in the analysis. Any value recorded only as above Upper Limit of Quantification (ULOQ) is set to ULOQ and included in the analysis.

Absolute values are 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 are flagged.

The derivation of a change from baseline in clinical chemistry and haematology at any post-baseline time point is presented in Section 3.3.1.3. Baseline values are derived as in Section 3.3.1.1.

Liver function tests are evaluated as multiples of the upper limit of the normal reference range (ULN). Participants who meet any of the following criteria at any time during the study is flagged:

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

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

4.5.3.2 Presentations

The absolute values and change from baseline in clinical chemistry and haematology variables are summarised descriptively (n, mean, SD, median, lower and upper quartile, minimum and maximum) over time.

Shift tables are produced to display low, normal and high level, defined based reference ranges provided by central laboratory, of each clinical chemistry and haematology variable at baseline and maximum/minimum post-baseline values.

Shift plots showing each individual participant's laboratory value at baseline and at maximum/minimum value post-baseline are 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 is also displayed on the shift plots.

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

For all participants who meet the biochemical criteria for Hy's Law (potential Hy's Law cases), the relevant laboratory variables are tabulated showing all visits for these participants. Participants with elevated ALT or AST in addition to elevated TBL at any time may be explored further graphically using individual participant profile plots.

All summaries and graphs report laboratory data in SI units and are produced for on-study period, as defined in Section [3.3.1.5](#)

4.5.4 Clinical Laboratory, Urinalysis

4.5.4.1 Definitions and Derivations

Urine samples are analysed locally and sent for analysis at the central laboratory only if a positive dipstick result for any parameter is observed. The urinalysis variables are specified in the CSP Table 12.

Baseline values are derived as in Section [3.3.1.1](#).

4.5.4.2 Presentations

Shift tables are generated to present changes from baseline to maximum value post-baseline. Tables are produced for on-study period, as defined in Section 3.3.1.5

4.5.5 Vital Signs

4.5.5.1 Definitions and Derivations

Vital signs include pulse rate, systolic blood pressure (BP), diastolic BP, respiratory rate, body temperature, body weight and body mass index (BMI, derived as presented in Section 4.1.5.1). Table 10 presents units and reference ranges. Absolute values and changes from baseline (where applicable) are compared to the relevant reference range, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the reference ranges are flagged.

The derivation of a change from baseline in vital signs at any post-baseline time point is presented in Section 3.3.1.3. Baseline vital signs are derived as in Section 3.3.1.1.

Table 10 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change from baseline criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (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	

4.5.5.2 Presentations

The absolute values and change from baseline in vital signs variables are summarised descriptively (n, mean, SD, median, lower and upper quartile, minimum and maximum) over time.

Shift plots showing each individual participant's vital signs value at baseline and at maximum/minimum value post-baseline are produced for each continuous vital signs variable.

All summaries and graphs are produced for on-study period, as defined in Section 3.3.1.5.

4.5.6 Electrocardiogram

4.5.6.1 Definitions and Derivations

The 12-lead digital ECG is performed locally at Visit 1 for all participants and at Visit 6, only if any new clinically significant ECG findings are found at Visit 1. The assessment are also performed locally at Visit 13 and IPD, only if the participant had a pre-existing cardiac condition, as determined at the discretion of the investigator.

4.5.6.2 Presentations

No separate summary of 12-lead digital ECG findings are produced.

4.5.7 Other Safety Assessments - Physical examination

4.5.7.1 Definitions and Derivations

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

4.5.7.2 Presentations

No separate summaries of physical examination findings are produced since there are no physical examination results reported outside of AE reporting.

5 INTERIM ANALYSIS

No interim analyses are planned in this trial.

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7 APPENDIX

7.1 Adverse events of special interest

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 are finalised by the study team prior to unblinding of the trial, and provided together with the study datasets at the time of submission.

AESIs defined based on MedDRA term

The following MedDRA term selection criteria is currently being used for defining the AESI:

- **Serious hypersensitivity reactions** – serious adverse events with narrow MedDRA SMQ of “Hypersensitivity” and modified anaphylactic reaction algorithm with a 72 hours time restriction (followed by medical review of the preferred terms identified as potential anaphylactic reactions, as well as any relevant supporting data)
- **Serious infections** serious adverse events with MedDRA System Organ Class of “Infections and infestations”
- **Malignancy** – based on SMQ “Malignant or unspecified tumours”
- **Guillain Barré Syndrome** – based on SMQ Guillan Barré syndrome
- **Serious cardiac events** – serious adverse events with MedDRA System Organ Class of “Cardiac disorders”
- **Helminth infections** – Helminth infections use an investigator-driven definition i.e., are directly determined from what is entered on the eCRF.
A participant is considered to have this AESI if the participant 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.
- **Adrenal Crisis** – Adrenal crisis is defined using a pre-specified list of high level and lower level MedDRA terms.

7.2 Maintenance therapy equivalence table - estimated daily doses for inhaled corticosteroids

Asthma Therapy	Total Daily Dose (µg/day)	
Inhaled Corticosteroid	Medium	High
Beclomethasone dipropionate (pMDI, standard particle HFA)	1000	>1000
Beclomethasone dipropionate (pMDI or DPI extrafine particle, HFA)	400	>400
Ciclesonide (pMDI, extrafine particle, HFA)	320	>320
Fluticasone furoate (DPI) eg, Arnuity® Ellipta®	n.a.	200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	500	>500
Budesonide (DPI, or pMDI, standard particle HFA)	800	>800
Mometasone furoate (pMDI, standard particle, HFA)	440	>440
Mometasone furoate (DPI)	Depends on DPI device – see product information	
Inhaled Corticosteroid in ICS/LABA combination ^a	Medium	High
Beclomethasone dipropionate (e.g. Fostair®)	400	>400
Fluticasone propionate HFA (e.g. Seretide®, Advair®)	500	>500

Asthma Therapy	Total Daily Dose (µg/day)	
	Medium	High
Inhaled Corticosteroid		
Fluticasone furoate (e.g. Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184-200
Budesonide, if as delivered dose (e.g. Symbicort®)	640	>640
Mometasone Furoate (e.g. Dulera®)	400	>400

^a The ICS doses for the ICS/LABA combinations were derived from GINA 2022 and using prescribing information.

For ICS doses with budesonide / LABA combinations that are given as metered doses, the medium to high dose classification is based on the upper section of the table above, which categorizes 800 ug/day as medium dose and >800 ug/day as high dose.

7.3 Maintenance therapy equivalence table - estimated OCS dose therapy

Oral Corticosteroid	Approximate equivalence dose
Prednisone	10 mg
Prednisolone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Betamethasone	1.2 mg
Dexamethasone	1.5 mg
Deflazacort	12 mg