Statistical Analysis Plan

Study Code	D5180C00009
Edition Number	3.0
Date	22nd October 2020

A Multicentre, Randomised, Double-Blind, Placebo Controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Reducing Oral Corticosteroid Use in Adults with Oral Corticosteroid Dependent Asthma (SOURCE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
AAER	Annualized asthma exacerbation rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
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
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood Pressure
CGIC	Clinical Global Impression of Change
COVID-19	Corona Virus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DBL	Database Lock
DAE	Adverse Event Leading to Discontinuation of Investigational Product
DBL	Database Lock
DL	Direct Likelihood
DNA	Deoxyribonucleic Acid
DRMI	Dropout Reason-based Multiple Imputation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment

Abbreviation or special term	Explanation
ePEF	Electronic Peak Expiratory Flow
ePRO	Electronic Patient Reported Outcome
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
FENO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GC	Common Glucocorticoid
GCP	Good Clinical Practice
GEE	Generalised Estimating Equation
GI	Gastrointestinal
GTI	Glucocorticoid Toxicity Index
HRU	Health Resource Utilization
ICS	Inhaled Corticosteroids
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
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
MACE	Major Adverse Cardiac Events
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random

Abbreviation or special term	Explanation
N/A	Not Applicable
nAb	Neutralizing Antibodies
NB	Negative Binomial
NC	Not Calculable
NQ	Non-quantifiable
OCS	Oral Corticosteroids
PD	Protocol Deviation
PEF	Peak Expiratory Flow
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
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
SCS	Systemic Corticosteroids
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
SNP	Single Nucleotide Polymorphism
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

Abbreviation or special term	Explanation
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
N/A	26Jun2018	Initially Approved SAP	Yes	
Whole document	22OCT2020	Links fixed.	N/A	Error in links resolved. No changes to the content.
Primary or secondary endpoints	16Sep2019	Sections 1.1.2 and 3.2.3.4: Supportive endpoint to the secondary endpoint has been updated from proportion of subjects with ≥1 asthma exacerbation to proportion of subjects who did not experience an asthma exacerbation over 48 weeks.	No	The endpoint was updated to align with the question of interest.
Primary or secondary endpoints	16Sep2019	Section 1.1.3: Neutralising antibodies (nAb) removed from immunogenicity endpoint.	Yes	The incidence of ADA is the key outcome measure for the immunogenicity evaluation. Other immunogenicity outcomes, including nAb are considered supportive.
Primary or secondary endpoints	16Sep2019	Sections 3.2.4.5 and 4.2.6.5: Additional endpoint for Asthma Symptom Diary (ASD) responders added.	N/A	Added to support the analysis of change from baseline in ASD
Primary or secondary endpoints	16Sep2019	Section 4.2.4.4: clarification of endpoint for Van Elteren test, and analysis of median percentage reduction in OCS added.	N/A	Analysis added to support the interpretation of the primary endpoint.
Derivation of primary or secondary endpoints	16Sep2019	Section 3.2.1.1: Derivation of final OCS dose in Table 2 updated to remove condition that stability may be after EOT visit.	N/A	Ensure consistency of derivation of endpoint for subjects entering the extension study from those who do not and continue follow-up visits in this study.
Derivation of primary or secondary endpoints	14Sep2020	Section 3.1.1: Baseline definition section updated to remove specific derivations, and ensure consistent approach taken for using last available measurement prior to randomisation or dosing.	N/A	Ensure consistency across baseline derivations.
Derivation of primary or secondary endpoints	14Sep2020	Section 3.1.2: Clarified therapy reasons included in and excluded from the daily OCS dose derivation. Specify calculations in case of overlapping doses.	N/A	Provide additional clarification of daily OCS dose derivation.
Derivation of primary	14Sep2020	Section 3.2.1.1: Final daily OCS dose derivation (Table 2)	N/A	Provide additional clarification on

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
or secondary endpoints		updated, including additional rule for subjects who discontinued IP following option 3 or withdrew from study due to COVID-19. Further clarification provided for the derivation of the different scenarios.		primary endpoint derivations, including the situation of COVID-19.
Primary or secondary endpoints	14Sep2020	Section 3.2.2.1: Added reference to the definition in the CSP.	Yes	Urgent care has been removed from the definition of supportive analyses, but it is the part of the definition used in the start and end dates.
Derivation of primary or secondary endpoints	14Sep2020	Section 3.2.2.1: Time at risk derivation updated to allow the date of last exacerbation status to be considered in derivation and remove the use of available visits prior to Visit 18 in determining the date of last exacerbation assessment.	N/A	To simplify the time at risk derivation.
Derivation of primary or secondary endpoints	14Sep2020	Sections 3.2.3.1, 3.2.3.3 and 4.2.5.4: Remove "Urgent Care" from supportive analyses of key secondary endpoint.	No	Provide clarification that only emergency room visit data is collected in the eCRF.
Derivation of primary or secondary endpoints	14Sep2020	Section 3.2.3.4: Clarification provided for supportive endpoint of proportion of subjects who did not experience an asthma exacerbation.	N/A	To provide clarification on derivation of completed treatment period and successful outcome.
Statistical analysis method for the primary or secondary endpoints	16Sep2019	Sections 4.2.4.2 and 4.2.5.2: Further clarification provided. Tipping point analyses added.	N/A	Following programming reviews. Recommendation from FDA.
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Section 4.2.4.2: Definition of treatment policy estimand includes all data in the planned treatment period.	N/A	Provide additional clarification and consistency of approach.
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Sections 4.2.4.2 and 4.2.5.2: Missing data imputation for primary and key secondary endpoint clarified and simplified.	N/A	To further clarify missing data imputation methodology and provide consistency of approach.
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Section 4.2.4.2: Clarify that subjects who discontinued IP and following option 3 will be assigned to placebo group in DRMI analysis.	N/A	Provide additional clarification and consistency of approach.
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Section 4.2.4.4: further clarification provided of the final daily OCS dose derivation for on-treatment analysis, including additional rule for subjects who discontinued IP (regardless of option) or withdrew from study due to	N/A	To clarify derivation for subjects affected by COVID-19 in analysis based on on-treatment period.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		COVID-19.		
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Section 4.2.4.4: Wilcoxon rank sum test used in analysis of percentage reduction in final daily OCS dose replaced by van Elteren test.	Yes	For consistency with Clinical Study Protocol.
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Section 4.2.5.2: Updated the algorithm so that for subjects with an imputed number of exacerbations after withdrawal, the offset will now exclude the time during any observed exacerbation and the 7 days following.	N/A	Provide additional clarification and consistency of approach.
Statistical analysis method for the primary or secondary endpoints	14Sep2020	Sections 4.2.4.1 and 4.2.5.1 Additional analysis for primary and key secondary endpoints will be conducted to assess the impact of the COVID-19 pandemic.	Yes (4.0)	To clarify how COVID-19 related data, introduced in CSP v4.0 (14 May 2020) will be presented.
Data presentations	16Sep2019	Section 2.2: Categories for grouping important protocol deviations updated.	N/A	For consistency with study Protocol Deviations Plan.
Data presentations	16Sep2019	Section 3.1.6: Visit windows updated to include bi-weekly windows for EQ-5D-5L and a visit window for variables collected on a sparse CSP schedule.	N/A	To allow data to be included in appropriate analysis timepoints.
Data presentations	16Sep2019	Section 3.1.7: definition of medications during the post-treatment period updated.	N/A	To only include new medication starting during this period
Data presentations	16Sep2019	Section 3.1.8: additional subgroup for FENO added. Clarification of derivation of IgE subgroup. Race subgroup updated to reflect eCRF categories. BMI subgroup updated to reflect general guidelines on BMI categories.	N/A	To clarify subgroup definitions.
Data presentations	16Sep2019	Section 3.1.9: section added to provide more information regarding derivation of endpoints for time to last dose of IP, and time to withdrawal from study.	N/A	To clarify derivation rules.
Data presentations	16Sep2019	Section 3.3.1: OCS compliance derivation added.	N/A	Required for CSR
Data presentations	16Sep2019	Section 3.3.2: Derivation of exposure AEs updated for AESIs.	N/A	In line with new AZ guideline on reporting safety data.
Data presentations	16Sep2019	Section 3.3.4: Values below the Lower Limit of Quantification (LLOQ) will be set to LLOQ, instead of LLOQ/2.	N/A	In line with new AZ guideline on reporting safety data.
Data presentations	16Sep2019	Section 4.2.6.5: statistical analysis of the daytime and night-time scores for ASD added.	N/A	Analysis added to support the interpretation of the ASD total score
Data presentations	16Sep2019	Section 4.2.8.1: further summaries of injection site reactions will be provided based on injection site and total	N/A	Required for CSR.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		doses of IP administered.		
Data presentations	16Sep2019	Sections 4.2.8.2, 4.2.8.3, 4.2.8.4 and 4.2.9.1: Updated to present visit based summaries over time using the on-study period instead of the on-treatment period.	N/A	Required for CSR
Data presentations	14Sep2020	Section 2.1.3: Addition of condition that subjects must have at least one sample with detectable drug levels to be included in the PK analysis set.	N/A	Provide additional clarification.
Data presentations	14Sep2020	Section 2.1.5: Removed text not referring to the on-treatment definition.	N/A	Remove redundant text.
Data presentations	14Sep2020	Section 2.2, 4.2.1, 4.2.3 and 4.2.8.1: Additional summaries will be conducted to assess the impact of the COVID-19 pandemic.	Yes (4.0)	To clarify how COVID-19 related data, introduced in CSP v4.0 (14 May 2020) will be presented.
Data presentations	14Sep2020	Section 2.2: Added the exception that PDs may lead to the exclusion of data for the PK analyses.	N/A	Provide additional clarification
Data presentations	14Sep2020	Section 3.1.1: Added text clarifying the definition of baseline for the PK data.	N/A	Provide additional clarification.
Data presentations	14Sep2020	Section 3.1.5 updated “Post-treatment” period to “Post-treatment/Follow-up” period and clarified the start date begins after the on-treatment period.	Yes	For consistency with programming reporting requirements and CSP amendment version 4.0 (14 May 2020).
Data presentations	14Sep2020	Section 3.1.6: Clarification of visit windows definition used to derive daily OCS dose over time.	N/A	To clarify derivation.
Data presentations	14Sep2020	Section 3.1.6: Clarified that any listings produced will include all data recorded, removed unnecessary text regarding the 16 week follow-up visit and noted how multiple ADA samples will be handled.	N/A	Provide additional clarification.
Data presentations	14Sep2020	Section 3.1.6: Visit windows table updated for Week 2 and Week 60.	Yes	For consistency with Schedule of Assessments in Clinical Study Protocol.
Data presentations	14Sep2020	Section 3.1.8: Definition of positive IgE panel, seasonal and perennial subgroups added. Removed baseline IgE status allergic/non-allergic as efficacy subgroup and added baseline perennial IgE status. Reference to IgE status updated to “specific IgE status (FEIA)”. Text describing baseline IgE status allergic/non-allergic	N/A	Required for CSR

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		changed to any FEIA positive/all FEIA negative.		
Data presentations	14Sep2020	Section 3.1.8: Changed age categories from adults (>65), adults (≥18 to ≤65) to adults (≥65), adults (≥18 to <65).	N/A	To be consistent with AZ standards.
Data presentations	14Sep2020	Section 3.1.9: Time to premature study withdrawal for subjects ongoing at primary DBL will be censored at last contact date rather than at Week 48.	N/A	Provides additional information of progress of ongoing subjects.
Data presentations	14Sep2020	Section 3.2.3.1: Clarification that the supporting endpoint in which hospitalisations and ER visits that are adjudicated to be asthma related are added, not adjudicated due to an asthma exacerbation.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 3.2.4.5: Clarification that individual items of ASD will be derived and reporting of data after Week 52.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 3.2.4.9: Changed daily asthma symptom total score to total asthma symptom score.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 3.2.4.13: Health care resource utilisation extended to include all data on study and clarified units are number of times or days, depending on the endpoint.	N/A	Required for CSR
Data presentations	14Sep2020	Sections 3.2.4.15 and 4.2.6.15: Clarified units to be used for reporting eosinophils and total serum IgE.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 3.2.5.5: Clarified that the immunoglobulin endpoints will be derived in the same manner as the laboratory data.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 3.2.4.9: “Asthma symptom score” changed to “Total daily asthma symptom score”. Text added to clarify that this is different from the total score derived from the ASD.	N/A	Provides clarity for TFLs and consistency with other project documents..
Data presentations	14Sep2020	Section 3.2.4.13: Health care resource utilisation extended to include all data on study and clarified that the unit may be number of times or days, depending on the endpoint.	N/A	Required for CSR
Data presentations	14Sep2020	Sections 3.2.4.15 and 4.2.6.15: Clarified units to be used for reporting eosinophils and total serum IgE.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 3.3.2: Addition of study adjusted incidence rate for adverse events.	N/A	Required for CSR
Data presentations	14Sep2020	Section 3.3.2: Derivation of exposure adjusted incidence rates.	N/A	In line with new AZ guideline on reporting safety data.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	14Sep2020	Section 4.2.2: Add additional summary of systemic corticosteroids by route of administration.	N/A	Required for CSR.
Data presentations	14Sep2020	Section 4.2.2: Added text noting that baseline total daily dose to be displayed will be the categories medium/high.	N/A	Provide additional clarification.
Data presentations	14Sep2020	Section 4.2.2: Added text regarding disallowed medications.	Yes	Provide additional clarification.
Data presentations	14-Sept-20	Section 4.2.4.2: Clarified that a few smaller increments in deltas for OCS can be applied if needed.	N/A	Provide additional clarification.
Data presentations	14Sep2020	Section 4.2.6.5: Clarified that graphical representation of adjusted daytime and night-time scores for ASD will be performed.	N/A	Provide additional clarification.
Data presentations	14Sep2020	Section 4.2.6.15: Noted that eosinophil and total serum IgE will also be included in the summaries of laboratory data.	N/A	Required for CSR
Data presentations	14Sep2020	Section 4.2.7: IgA, IgG and IgM data will be included in the summaries of laboratory data.	N/A	Required for CSR.
Data presentations	14Sep2020	Section 4.2.7: Removed text regarding summaries of total and specific immunoglobulin endpoints.	N/A	Specific IgE data are only available at baseline. Total IgE data are described in other section.
Data presentations	14Sep2020	Section 4.2.7: New text added to describe summaries of serum biomarker available at primary DBL.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 4.2.8.1: AE summaries for causality and maximum intensity will be reported by PT only, and not SOC and PT.	N/A	For consistency with AZ standards.
Data presentations	14Sep2020	Section 4.2.8.2: Removed figure of mean changes from baseline and clarify that all summaries and figures will report laboratory data in SI units.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Sections 4.2.8.2 and 4.2.8.3: Shift tables will not display missing values. Shift plots will not present reference lines for normal ranges.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 4.2.9.1: Clarified data to be included in the summary of serum tezepelumab concentrations.	N/A	Provides clarity for TFLs.
Data presentations	14Sep2020	Section 4.2.9.1: Added non-treatment-emergent ADA positive.	N/A	Required for CSR.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	14Sep2020	Section 4.2.9.2: Clarified that the evaluation of ADA impact on primary endpoint, key secondary endpoint and safety outcomes will be assessed only on individual basis and in subjects ADA positive only.	N/A	Required for CSR.
Other	16Sep2019	Sections 1.2 and 1.3: Number of subjects updated from 140 randomised subjects to 152 randomised subjects, and proportion of subjects in ≥300 eosinophil/µL updated from 30% to 35%.	Yes (V3.0)	The increase in sample size allows for an increase in the proportion of subjects in ≥300 eosinophil/µL while maintaining the number of subjects in <300 eosinophil/µL.
Other	16Sep2019	Reference to DBL updated to primary DBL in the following sections: Section 2.1.4: updated to change reference from database lock (DBL) to primary DBL. Section 3.1.5: definition of on-study period updated to reflect primary DBL.	Yes (V3.0)	To accommodate a planned additional database lock once the last subject completes treatment phase (week 48).
Other	16Sep2019	Sections 1.1.5, 3.2.5.1 and 4.2.7: Exploratory endpoint added for mean daily exposure of systemic corticosteroids over 48 weeks.	N/A	Allow for assessment of the total systemic corticosteroid load over time for each treatment group.
Other	16Sep2019	Sections 3.2.5.3 and 4.2.7: Additional endpoint for SGRQ deterioration added.	N/A	Added to support the analysis of change from baseline in SGRQ
Other	16Sep2019	Section 6: updated to remove changes which have been incorporated in revised CSP since V1.0 of SAP.	Yes (V3.0)	Following revision to CSP.
Other	14Sep2020	Sections 1.1.3, 3.4 and 4.2.9.1: Removed the word trough from the endpoint, serum trough concentrations.	No	To provide additional clarification as not only trough concentrations will be summarised.
Other	14Sep2020	Sections 1.1.5 and 3.2.5.5: Exploratory endpoint of allergen specific IgE removed.	Yes (V4.0)	CSP amendment version 4.0 (14 May 2020).
Other	14Sep2020	Section 1.1.5: Exploratory endpoint of total IgE levels removed.	No	Already covered in Section 1.1.3 and 3.2.4.15.
Other	14Sep2020	Sections 1.1.5, 3.1.8: Reference to IgE status updated to “specific IgE status (FEIA)”.	Yes (V3.0)	Ensure consistency of text in SAP
Other	14Sep2020	Section 1.2: Text updated to state that the follow-up period may not apply to subjects who participate in the extension study.	Yes (V4.0)	CSP amendment version 4.0 (14 May 2020) .
Other	14Sep2020	Section 2.1.5: Removed text not referring to the on-treatment definition.	N/A	Remove redundant text.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	14Sep2020	Section 2.2: Clarified only not fulfilling key eligibility criteria will be considered important PDs.	No	Consistent with Protocol Deviation plan.
Other	14Sep2020	Section 3.2.4.5: Means derived for individual symptom scores within the ASD will combine daytime and night-time data.	N/A	Provides clarity for TFLs. `
Other	14Sep2020	Section 3.2.5.1: Clarification that SCS taken for asthma reason with therapy reason "Other" with additional information that this was taken due to adrenal insufficiency will be included in the calculation. All SCS doses will be converted to prednisone equivalent dose.	N/A	To further clarify the derivation of SCS taken for asthma reason.
Other	14Sep2020	Sections 3.2.5.4 and 4.2.7: Percentage of symptomatic days will be presented instead of non-symptomatic days.	N/A	Preference for reporting of endpoint
Other	14Sep2020	Section 3.2.5.7: Added derivation for serum biomarker data.	N/A	Required for CSR
Other	14Sep2020	Sections 3.3.2 and 4.2.8.3: Treatment-emergent text replaced with "during on-treatment period".	N/A	For consistency with reporting periods.
Other	14Sep2020	Sections 3.3.6 and 4.2.8.4: Changed ECG to digital ECG.	Yes	Consistency with protocol.
Other	14Sep2020	Section 4.2.4.5: The minimal number of subjects required in subgroup was specified. If the criteria not met, the subgroup will be excluded from the analysis.	N/A	To clearly specify rules for TFLs.
Other	14Sep2020	Section 4.2.4.3: Clarification that SCS taken for non-asthma reason with therapy reason "Other" with additional information that this was taken due to adrenal insufficiency will be excluded in the calculation of SCS. All SCS doses will be converted to prednisone equivalent dose.	N/A	To further clarify the derivation of SCS taken for non-asthma reason.
Other	14Sep2020	Section 6: Updated to remove changes which have been incorporated in revised CSP since V1.0 of SAP or add new changes.	Yes (V4.0)	Following revision to CSP.
Other	14Sep2020	Appendix 8.3: Added to include therapy equivalent tables for ICS and OCS therapy.	Yes (V3.0)	Additional row for Budesonide as a metered dose added to table in CSP
Other	14Sep2020	Appendix 8.4: Includes description of additional analysis conducted to assess the impact of the COVID-19 pandemic.	Yes (V4.0)	To clarify how COVID-19 related data, introduced in CSP v4.0 (14 May 2020) will be presented.

1. STUDY DETAILS

This statistical analysis plan (SAP) for study D5180C00009 outlines the statistical analyses specified in the latest version of the Clinical Study Protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

1.1 Study objectives

1.1.1 Primary objective

Objective:	Endpoint/variable:
To evaluate the effect of tezepelumab compared with placebo in reducing the prescribed OCS maintenance dose in subjects with asthma requiring chronic treatment with maintenance OCS in addition to high dose ICS plus LABA	**Primary outcome variable:** Categorized percent reduction from baseline in the daily OCS dose at Week 48 while not losing asthma control The categories for percent change from baseline in daily OCS dose are defined as: 1. ≥90% to ≤100% reduction 2. ≥75% to <90% reduction 3. ≥50% to <75% reduction 4. >0% to <50% reduction 5. no change or any increase **Primary outcome measure:** Cumulative odds ratio vs placebo at Week 48

1.1.2 Key secondary objectives

Objectives:	Endpoint/variable:
To evaluate the effect of tezepelumab compared with placebo on asthma exacerbations	**Key secondary outcome variable:** Annualised asthma exacerbation rate (AAER) **Outcome measure:** AAER ratio vs placebo over 48 weeks **Supportive outcome variable:** Time to first asthma exacerbation **Outcome measure:** Asthma exacerbation hazard ratio vs placebo over 48 weeks **Supportive outcome variable:** Rate of asthma exacerbation associated with ER visit, urgent care visit or hospitalisation **Outcome measure:** AAER ratio vs placebo over 48 weeks **Supportive outcome variable:** Proportion of subjects who did not experience an asthma exacerbation over 48 weeks **Outcome measure:** Odds ratios vs placebo at Week 48

1.1.3 Other secondary objectives

Objectives:	Endpoint/variable:
To evaluate the effect of tezepelumab compared with placebo on the prescribed OCS daily maintenance dose	**Outcome variables:** • Proportion of subjects with 100% reduction from baseline in daily OCS dose at Week 48 • Proportion of subjects with daily OCS dose ≤5 mg at Week 48 • Proportion of subjects with ≥50% reduction from baseline in daily OCS dose at Week 48 **Outcome measure:** Odds ratios vs placebo at Week 48
To evaluate the effect of tezepelumab compared with placebo on Pre-BD lung function	**Outcome variables:** Change from baseline in Pre-BD forced expiratory volume in 1 second (FEV_1) **Outcome measure:** Mean difference vs placebo at Week 48
To assess the effect of tezepelumab compared with placebo with regards to asthma symptoms and other asthma control metrics	**Outcome variables:** Change from baseline in: • Weekly mean daily Asthma Symptom Diary Score as captured in the daily Asthma Symptom Diary (ASD) • Weekly mean rescue medication use • Weekly mean home peak expiratory flow (morning and evening) • Weekly mean number of night-time awakening due to asthma • Asthma Control Questionnaire 6 (ACQ-6) score **Outcome measure:** Mean difference vs placebo at Week 48
To assess the effect of tezepelumab compared with placebo with regards to asthma related and general health-related quality of life	**Outcome variables:** Change from baseline in: • Standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(s)+12) total score • European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score **Outcome measure:** Mean difference vs placebo at Week 48
To evaluate the efficacy of tezepelumab compared with placebo on health resource utilization and productivity loss due to asthma	**Outcome variables:** • Number of asthma specific resource utilizations (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma

Objectives:	Endpoint/variable:
	medications) • Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire (WPAI+CIQ) score **Outcome measures:** • Difference in number of asthma specific resource utilizations vs placebo over 48 weeks • Difference in WPAI+CIQ score vs placebo at Week 48
To assess the effect of tezepelumab on biomarkers	**Outcome variable:** Change from baseline in FENO, peripheral blood eosinophils and total IgE **Outcome measure:** Mean difference vs placebo at Week 48
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	**PK:** Serum concentrations **Immunogenicity:** Incidence of anti-drug antibodies (ADA)

1.1.4 Safety objectives

Objectives:	Endpoint/variable:
To evaluate the safety and tolerability of tezepelumab	• Adverse events/serious adverse events • Vital signs • Clinical chemistry/haematology/urinalysis parameters • Digital electrocardiograms
To evaluate the effect of tezepelumab on glucocorticoid toxicity	Glucocorticoid toxicity index

1.1.5 Exploratory objectives

Objectives:	Endpoint/variable:
CCI	

Objectives:	Endpoint/variable:
	CCI

1.2 Study design

This is a multicentre, randomised, double-blind, parallel group, placebo-controlled Phase 3 study designed to evaluate the efficacy and safety of a fixed 210 mg dose of tezepelumab administered subcutaneously (SC) every 4 weeks (Q4W) versus placebo in reducing OCS use in adult subjects with asthma requiring treatment with maintenance OCS in combination with high-dose ICS plus LABA with or without other asthma controller therapy, while maintaining asthma control.

Approximately 152 subjects will be randomised globally from about 65-75 study sites in a 1:1 ratio to either:

- tezepelumab 210 mg every 4 weeks (Q4W) by SC injection, or
- placebo Q4W by SC injection.

The subjects will be stratified by region (Western Europe and North America; Central/Eastern Europe; Rest of World).

The randomised study population will be monitored throughout recruitment overall and by region and eosinophil level at enrolment (approximately 35% of subjects with ≥300 eosinophils/μL). Limits may be placed on subsequent randomisation of subjects with eosinophil values < 300 eosinophils/μL if necessary, to achieve this target.

After the initial enrolment (Visit 1) and confirmation of entry criteria, all subjects will enter a 2-week run-in period to allow adequate time for all of the eligibility criteria to be evaluated plus an up to 8-week optimization phase to establish, by dose titration every two weeks, a minimum effective dose of the prescribed OCS. The optimization phase may be extended to account for treatment of an exacerbation to allow for 2-weeks of a stable OCS dose prior to randomisation. The criteria for the adjustment of the OCS dose are described in Section 8.1.1 of the CSP.

After the OCS optimization phase, subjects who fulfil the eligibility criteria will be randomised (Visit 6) to a 48-week treatment period.

There are 3 phases in the 48-week treatment period following randomisation where subjects will be administered study drug.

- Induction phase – from visit 6 (week 0) to the day prior to visit 7 (week 4) when subjects should remain on their optimized OCS dose.

- OCS reduction phase – from visit 7 (week 4) to the day prior to visit 16 (week 40) when OCS dose reduction should be started at week 4 with the possibility of dose titration every 4 weeks. No down-titration after week 36.

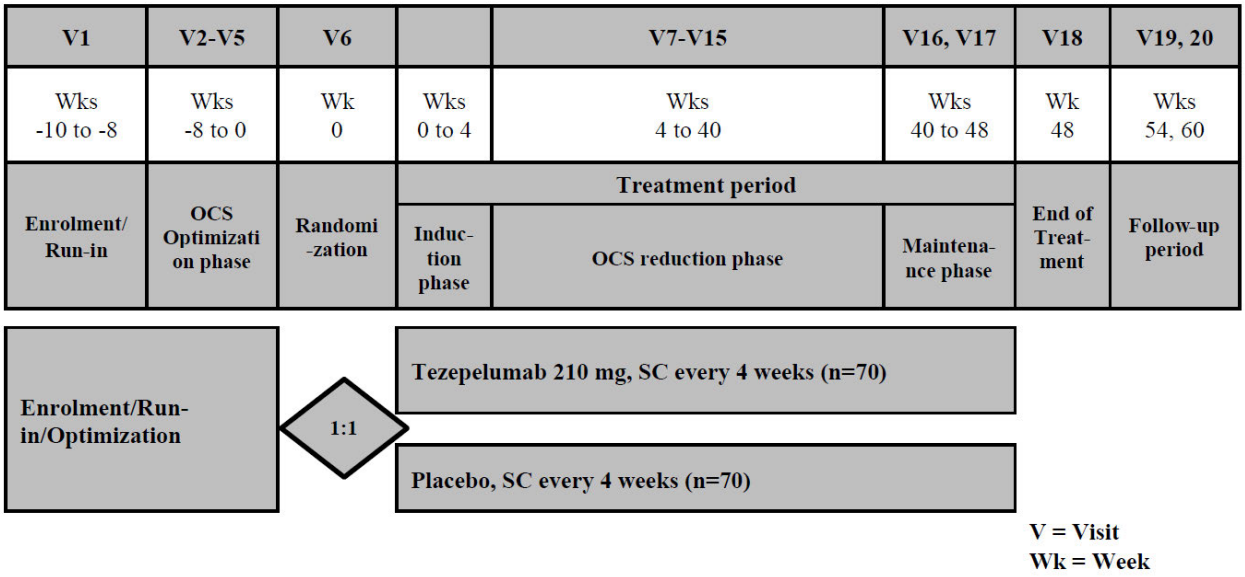
- Maintenance phase – from visit 16 (week 40) to visit 18 (week 48) when subjects should remain on the OCS dose reached at week 40 (or earlier if OCS dose reduction failed because of clinical deterioration or if lowest possible OCS dose was determined before week 40) or remain on complete oral corticosteroid elimination if possible.

The last dose of tezepelumab or placebo will be given at week 44 with end of treatment (EOT) visit at Week 48. IP will not be administered at Week 48. There are up to 18 visits from screening to scheduled end of treatment, followed by two safety follow-up visits performed at Week 54 and at Week 60.

Subjects completing the planned treatment period may be eligible to enrol in a separate extension study and these subjects may not attend the follow up visit at Week 54 and Week 60. Any data collected after a subject is enrolled into the separate extension study will not be included in the analyses described in this SAP.

A graphical view of the study is shown in Figure 1 below.

Figure 1 Study Design



Note: The visit at week 48 is part of the maintenance phase.

Subjects should preferably be maintained on their currently prescribed ICS plus LABA with or without other asthma controller therapy, without changes, from 3 months before screening until end of study.

See CSP Section 1.1, Tables 1 and 2 for a detailed list of visits and assessments.

Subjects who prematurely discontinue investigational product (IP) during the study will be encouraged to undergo scheduled study visits/procedures for the full 48-week period. At the investigational product discontinuation (IPD) visit the subject will be given three following options (further details are provided in CSP Section 7.1.1):

- *Option 1*: The subject should be encouraged to return to all regular clinic visits and perform all assessments as per schedule of assessment (SoA) until scheduled EOT visit at Week 48 (+/-5 days).

- *Option 2*: If the subject cannot comply or does not wish to comply with option 1 above, the subject will be offered the option of follow-up on a monthly basis via telephone calls while continuing at-home eDiary and electronic peak expiratory flow (ePEF) completion including the questionnaires that otherwise would have been completed at the site as per SoA. This option would be followed by an on-site EOT visit at Week 48 (+/-5 days).

- *Option 3*: If the subject cannot comply or does not wish to comply with options 1 or 2 above, the subject will be offered the option of being contacted via telephone at the scheduled EOT visit at Week 48 (+/-5 days).

1.3 Number of subjects

Approximately 152 subjects will be randomly assigned to study treatment using 1:1 allocation between the two treatments. Since the primary analysis of the primary endpoint will include all randomised subjects as far as possible, no need is envisaged to adjust the number of subjects planned to be randomised in order to obtain a number of evaluable subjects.

With 76 subjects per treatment group it is estimated that, using a 2-sided 5% significance level, the power to reject the null hypothesis for the primary endpoint of OCS reduction will be at least 90%, assuming:

- An odds ratio of 2.75 and the proportional odds assumption (see Section 4.1.1)

The proportion of subjects in the 5 different dose reduction categories is similar to results reported in the Steroid Reduction with Mepolizumab Study (Bel et al 2014).

The following proportions have been assumed for placebo:

  - Category 1 (90% - 100% reduction): 10% of subjects
  - Category 2 (75% - <90% reduction): 10% of subjects
  - Category 3 (50% - <75% reduction): 15% of subjects
  - Category 4 (>0% - <50% reduction): 15% of subjects
  - Category 5 (no reduction or an increase): 50% of subjects

The minimal detectable odds ratio still being significant with the above assumptions is 1.86.

For the key secondary endpoint of reduction in the AAER, 76 subjects per group has >80% power to reject the null hypothesis for rate ratios up to 0.39, using a 2-sided 5% significance level, and assuming:

- A placebo rate of 1.3 exacerbations/year in this study population
- A conservative assumption on the dispersion parameter (2.4)
- Uniform dropout of 10%

2. ANALYSIS SETS

2.1 Definition of analysis sets

All subjects analysis set

This analysis set comprises all enrolled subjects who signed the informed consent form and will be used for reporting of disposition and screening failures.

Randomised subjects analysis set

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

2.1.1 Efficacy analysis set

Full analysis set (FAS)

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

Efficacy analyses will be performed using all subjects in the FAS, according to the intent-to-treat (ITT) principle. Subjects will be analysed according to their randomised treatment (including in the case of any discrepancies between randomised and actual treatment).

The FAS specifies which subjects are included in efficacy analyses. Details of which data are included in efficacy analyses for these subjects are given in the respective sections, notably in Section 2.1.5, Section 3.1.5 and Section 4.2.

For consistency with efficacy analyses, demographics and baseline characteristics will be summarised using the FAS.

2.1.2 Safety analysis set

Safety analysis set

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

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

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

Summaries of anti-drug antibodies (ADA) will also be based on the safety analysis set, using the same approach to handle treatment dispensing errors.

2.1.3 Other analysis set

PK analysis set

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

2.1.4 Handling of other issues which may impact analysis sets

If it is found that any subject has been randomised on more than one occasion (contrary to the protocol) under different subject numbers, either at the same site or at different sites, then data corresponding to the first subject participation will be used in the analyses. Data associated with the second (and any subsequent) participation of the same subject will be listed and discussed in the CSR. All data associated with duplicate randomisations will be reviewed, and decisions regarding the analysis and reporting of this data will be documented, prior to unblinding at the primary database lock.

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

2.1.5 Definition of on-treatment

Efficacy analyses

Any efficacy assessment date which occurs between the date of randomisation and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal) will be considered on-treatment, where the date of study withdrawal is the completion or discontinuation date from the “Disposition” eCRF page, where any subject status other than “Completed” has been entered. In particular, this allows a subject who completes treatment according to the protocol to have their Week 48 data included as on-treatment, provided Week 48 is within the protocol visit window after the last dose of IP at Week 44.

Safety analyses

Safety analyses will be presented for subjects in the safety analysis set, which is describe further in Section 2.1.2.

For this purpose, any adverse event start date, or any safety assessment date (e.g. laboratory, vital signs), which occurs between the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal) will be considered on-treatment. In particular, this allows inclusion of any safety-related information which may be reported at or generated from the IPD visit to be considered as on-treatment, provided the IPD visit is within the protocol visit window after premature discontinuation of IP.

2.2 Violations and deviations

Only important protocol deviations (PDs) will be listed and tabulated in the CSR, and only for randomised subjects (not screening failures). These are defined as PDs which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a subject's rights, safety or well-being. Important PDs in this trial will be grouped under one of the following categories:

- Did not fulfil key eligibility criteria
- Developed discontinuation criteria but continued IP
- Received prohibited concomitant medication
- Non-compliance with restrictions during the study
- Protocol-required procedure not adhered to
- IP Management issues
- GCP violation deviation
- Safety Reporting deviations and other safety

Additional summaries assessing the impact of the COVID-19 pandemic will be provided as described in Appendix 8.4.

All important PDs will be 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 will be monitored (blinded) during the trial, to allow for retraining of Investigators about protocol defined methods if applicable to prevent further PDs.

With the exception of the PK analyses, important PDs will not be used to exclude any subject from the analysis set, nor to exclude any data from subjects included in an analysis set.

The study PD Plan outlines the management of PDs and includes the proposed categories of PDs in this trail. Any PDs which are not defined as important will not be reported and discussed in the CSR.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Definition of baseline

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

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

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

The baseline OCS dose is derived as the most recent prescribed, daily OCS dose prior to randomisation (Visit 6) i.e. the daily dose regimen that a subject is prescribed at the time of randomization (see Section 3.1.2). If the OCS dose is administered every other day, the total OCS dose over the two days will be totalled and averaged (see Section 3.1.2 for further details).

For weekly mean scores derived from subject eDiary (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 will be 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.

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

For safety variables (vital signs, weight/BMI, haematology, clinical chemistry, urinalysis, 12-lead digital ECG), baseline will be defined as the latest non-missing assessment prior to first

dose. If no time is recorded for an assessment, and the assessment takes place at Visit 6, this will be assumed to be a pre-dose assessment.

3.1.2 Daily OCS dose

Unless specified otherwise, the daily 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.

Maintenance dose of OCS is collected on the SYSTCORT eCRF page with a therapy reason of "Maintenance dose", "Titration, due to asthma" and "Other" with additional information that this was taken due to adrenal insufficiency. If the OCS doses with more than one therapy reasons are prescribed on the same day (e.g. "Maintenance dose" and in addition "Other: AI"), then the sum of the doses will be calculated.

The prescribed OCS dose with therapy reason of "Asthma exacerbation per protocol" or "Worsening of asthma, without exacerbation" will not be included in the daily OCS dose calculation. In case of overlapping OCS doses taken for asthma worsening or exacerbation with maintenance doses of OCS, the latter one will be excluded from the daily OCS dose calculation.

If the subject is on a fixed daily dose, then the OCS dose is defined as that prescribed dose. If the subject is on an 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 subject be on a 10 mg every other day regimen of OCS, their OCS dose will be defined as 5 mg.

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 will also be set to missing.

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

3.1.4 Reversibility

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

$$\%Reversibility = [(Post\text{-}BD\ FEV_1 - Pre\text{-}BD\ FEV_1)/Pre\text{-}BD\ FEV_1] \times 100\%$$

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

3.1.5 Study periods

The following study periods are defined for analysis purposes:

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

Optimization period: starting on the date of Visit 2 and ending one day prior to randomisation (for randomised subjects) or on the date of the last study procedure (for screening failures). If any subject is re-screened, the latest available screening will be used for this purpose.

Planned treatment period (on-treatment and off-treatment): starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the date of the Week 48 visit or earlier study withdrawal date (for subjects not followed up until Week 48).

On-treatment period: starting and ending on the start and end dates defined in Section 2.1.5 for efficacy and safety analyses, respectively.

Post-treatment period/Follow-up period: starting one day after the end date of on-treatment period, defined in Section 2.1.5 for efficacy and safety analyses, respectively, and ending on the study completion or withdrawal date. Note: For subjects entering the separate extension study, the study completion date will be the day of enrolment in the extension study.

On-study period (planned treatment and follow-up): starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the study completion or withdrawal date. Note: for subjects entering the extension study, the study completion date will be the day of enrolment in the extension study. 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).

3.1.6 Visit windows

Summaries and analyses, both efficacy and safety, which are presented by time point (e.g. “Week 48”) will 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 (notably the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

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

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

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

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

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

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

- The non-missing value closest to the target day will be selected for analysis at that visit
- If two non-missing values are the same distance from the target day, the earlier of the two values will be selected for analysis at that visit
- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time will be selected for analysis at that visit.
- If two non-missing values (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 will be selected for analysis at that visit. For categorical variables in this situation, the worst case will be 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 subject has no value within a particular visit window, then the subject will have a missing value at that visit in summaries and analysis.

The same visit window definitions below will be used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.1.5). In practice, each data record in the planned treatment period will be first identified, and then further flagged according to whether it is on-treatment or off-treatment. This flag will be used to

select all eligible records for subsequent visit windowing, according to whether the derived visits are to be used in a planned treatment 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 1 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 will be 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 will be used for those variables for which the most sparse scheduling is planned in the protocol. These variables are: weight, GTI, WPAI+CIQ scores, SGRQ score, and post-BD spirometry.

Visit windows presented in Table 1 will not be applied for calculation of daily OCS dose at each timepoint. The OCS dose at each week will be based on actual visit dates to account for changes in OCS dose at scheduled visit. The daily OCS dose at Visit X will be the latest OCS dose during the period from Visit (X-1) date + 2 days until Visit X date + 1 day. For Week 48, the daily OCS dose will be the latest OCS dose during the period from Visit 17 date + 2 days until the Visit 18 date.

Table 1 Visit Windows

Time Point	Target Day	Visit Window 1 (full visit schedule)	Visit Window 2 (EQ-5D-5L)	Visit Window 3 (sparse CSP schedule)
Baseline (Week 0)	1	See Section 3.1.1 for baseline definitions		
Week 2	15	N/A	2-21	N/A
Week 4	29	2-42	22-35	2-56
Week 6	43	N/A	36-49	N/A
Week 8	57	43-70	50-63	N/A
Week 10	71	N/A	64-77	N/A
Week 12	85	71-98	78-91	N/A
Week 14	99	N/A	92-105	N/A
Week 16	113	99-126	106-119	N/A
Week 18	127	N/A	120-133	N/A

Time Point	Target Day	Visit Window 1 (full visit schedule)	Visit Window 2 (EQ-5D-5L)	Visit Window 3 (sparse CSP schedule)
Week 20	141	127-154	134-147	N/A
Week 22	155	N/A	148-161	N/A
Week 24	169	155-182	162-175	141-196
Week 26	183	N/A	176-189	N/A
Week 28	197	183-210	190-203	N/A
Week 30	211	N/A	204-217	N/A
Week 32	225	211-238	218-231	N/A
Week 34	239	N/A	232-245	N/A
Week 36	253	239-266	246-259	N/A
Week 38	267	N/A	260-273	N/A
Week 40	281	267-294	274-287	N/A
Week 42	295	N/A	288-301	N/A
Week 44	309	295-322	302-315	N/A
Week 46	323	N/A	316-329	N/A
Week 48	337	323-350	330-343	309-364
Follow-up Week 54	379	351-399	N/A	N/A
Follow-up Week 60	421	400-441	N/A	N/A

N/A – Not Applicable

In all cases above, no time points will be 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 will include all scheduled and unscheduled visits, including derived weekly means for data recorded beyond the final scheduled visit for all subjects randomised.

Data from the separate extension study (for participating subjects) will not be used for any of the visit window classifications above.

Finally, it should be noted that a visit window approach will not be used for data captured on a device daily by the subject, which will be aggregated for analysis at each relevant time point

by using a weekly mean or similar approach. For this purpose, the definition of the weekly mean is provided in the relevant endpoint derivation sections of this SAP.

3.1.7 Prior and concomitant medication

Medications taken by any subject at any time during the study will be coded using the ATC classification system within the WHO Drug Dictionary.

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

- Prior medications:
  - end date ≤ date of first dose of IP
- Concomitant medications during on-treatment period:
  - end date > date of first dose of IP and start date ≤ minimum(date of last dose of IP + 33 days; date of death, date of study withdrawal), or
  - end date ongoing and start date ≤ minimum(date of last dose of IP + 33 days, date of death, date of study withdrawal)
- Concomitant medications during post-treatment period (for subjects still being followed up then):
  - start date > date of last dose of IP + 33 days

Essentially the above says that:

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

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

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

has a partially missing end date (month/year or year only) which is the same as that for end of IP treatment, it will be assumed to have ended post-treatment. Note: For subjects entering the separate extension study, the study completion date will be the day of enrolment in the extension study.

3.1.7.1 Systemic corticosteroid medication

Systemic corticosteroid medication collected in the SYSTCORT eCRF page will be considered separately from prior and concomitant medications described above. See sections 3.2.1.1, 3.2.5.1 and 4.2.7 for further details.

3.1.8 Definition of subgroups

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

- * Baseline eosinophils group: <300/µL, ≥300/µL
- * Baseline eosinophils group: <150/µL, ≥150/µL
- Baseline eosinophils group: <150/µL, ≥ 150/µL to < 300/µL, ≥ 300/µL to <450/µL, ≥ 450/µL
- * Baseline clinic visit FENO group: < 25ppb, ≥ 25ppb
- Baseline clinic visit FENO group: <25ppb, 25 to <50ppb, ≥50ppb
- Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA
  - "Any FEIA positive" requires 1 or more specific IgE panels using fluorescent enzyme immunoassay (FEIA) to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 12 panels to be available.
  - "All FEIA negative" requires all 12 specific IgE panels to be negative. If there are fewer than 12 panels with data available and none of these is positive, then IgE status is considered "Unknown FEIA".
  - Positive is defined as a value ≥0.35 kU/L.
- * Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA
  - "Any perennial FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 8 panels to be available.

  - "All perennial FEIA negative" requires all 8 specific IgE panels to be negative. If there are fewer than 8 panels with data available and none of these is positive, then IgE status is considered "Unknown perennial FEIA".

  - Positive is defined as a value ≥0.35 kU/L.

  - The 8 panels include: American Cockroach, Cat Dander, D. farina, D. pteronyssinus, Dog Dander, German Cockroach, Mould Mix, Oriental Cockroach.

- Baseline specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA

  - "Any seasonal FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 4 panels to be available.

  - "All seasonal FEIA negative" requires all 4 specific IgE panels to be negative. If there are fewer than 4 panels with data available and none of these is positive, then IgE status is considered "Unknown seasonal FEIA".

  - Positive is defined as a value ≥0.35 kU/L.

  - The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.

- * Daily OCS dose at baseline: (≤10 mg versus >10 mg prednisone or prednisolone)

- * Age category: age (≥18 to <65) and age (≥65)

- * Gender: Male/Female

- Race: White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other

- Baseline body mass index (BMI): <18.5 kg/m^2, 18.5 to <25.0 kg/m^2, 25.0 to <30.0 kg/m^2, ≥30.0 kg/m^2

- * Baseline body mass index (BMI): <30 kg/m^2, ≥30 kg/m^2

- * Geographical region: Western Europe and North America (incl. Germany and USA); Central/Eastern Europe (incl. Poland, Turkey and Ukraine); Rest of World (incl. Argentina and South Korea).

- Country

3.1.9 Disposition

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

Time to last dose of IP

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

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

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

Time to premature study withdrawal

Time to premature study withdrawal will be defined as follows:

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

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

Subjects who did not prematurely withdraw from study will be censored at one of the following dates:

- Completion or discontinuation date from the "Disposition" eCRF page, where subject status of "Completed" has been entered.
- At primary DBL, ongoing subjects will be censored at their last contact date.

3.2 Derivation of efficacy variables

3.2.1 Primary endpoint

3.2.1.1 Categorized percent reduction from baseline in the daily OCS at Week 48 while not losing asthma control

The primary endpoint is the percentage reduction from baseline in daily OCS dose at 48 weeks or earlier whilst not losing asthma control, by defined categories below, where percent change from baseline is defined as:

*((final daily OCS dose – baseline daily OCS dose) / baseline daily OCS dose) * 100.*

Percent change from baseline in the final daily OCS dose at Week 48 while not losing asthma control will then be categorized into five categories defined as:

- *Category 1*: ≥90% to ≤100% reduction
- *Category 2*: ≥75% to <90% reduction
- *Category 3*: ≥50% to <75% reduction
- *Category 4*: >0% to <50% reduction
- *Category 5*: no change or any increase

Should a subject be placed on a regimen of OCS where different amounts are to be taken each day, their baseline and/or final dose will be defined as the average daily dose, as in Section 0.

The baseline OCS dose is described in Section 3.1.1. Final daily OCS dose will be derived as described in Table 2 below. Post IP discontinuation data from subjects choosing and remaining on follow-up option 1 and 2 (see Section 1.2) will be included in the primary analysis. Any data collected for subjects discontinued IP choosing option 3 will be censored at the time of IP discontinuation. The last selected option by subject will be used in the final OCS dose derivation. No data after Week 48 will be included in the final OCS dose derivation.

Table 2 Derivation of final daily OCS dose

Situation		Final daily OCS Dose
• Premature withdrawal from study due to reason other than COVID-19 • Premature discontinuation of IP due to reason other than COVID-19 and following option 3		Final daily OCS dose = Last reported OCS dose[a] received by subject with asthma stability verified[b] at the time of study withdrawal or IP discontinuation, and increased by 1 dose level as indicated in Table 3. If this is not available, then Final dose = OCS dose[a] at baseline increased by 1 dose level higher from Table 3.
• Premature withdrawal from study due to COVID-19 • Premature discontinuation of IP due to COVID-19 and following option 3		Final daily OCS dose = Last reported OCS dose[a] received by subject with asthma stability verified[b] at the time of study withdrawal or IP discontinuation due to COVID-19. If this is not available, then Final dose = OCS dose[a] at baseline.
• Premature discontinuation of IP and following option 1 or 2 • No premature discontinuation of IP	No asthma deterioration[c] during maintenance phase	Final daily OCS dose = Last reported OCS dose level
	Asthma deteriorates[c] during maintenance phase	Final dose = Last reported OCS dose[a] received by subject with asthma stability verified[b] after the end of the deterioration. If data regarding asthma stability after the end of the deterioration is not available, then the final daily OCS dose should be the latest OCS dose[a] received by subject with asthma stability and increased by 1 dose level as indicated in Table 3.

[a] daily OCS dose is based on information collected in SYSTCORT eCRF.
[b] Asthma stability is defined as no change in OCS dose for at least 2 weeks.
[c] Deterioration is defined as reporting a protocol defined exacerbation in the EXACATE eCRF module, or has systemic corticosteroids recorded in the SYSTCORT eCRF module with reason "Worsening of asthma, without exacerbation")

Table 3 OCS dose titration

Latest OCS dose	Increment
<10 mg	2.5 mg
≥10 mg	5 mg

Data from Table 9 in Clinical Study Protocol

3.2.2 Key secondary endpoint

3.2.2.1 Annualized asthma exacerbation rate (AAER)

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 (at a dose at least 1 level higher than the current titration step) for at least 3 consecutive days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day bolus/burst of systemic corticosteroids. **Note:** Per protocol up titration of OCS dose to 1 level higher (as described in Table 9 of the CSP) is not considered an exacerbation per se.

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

Two or more exacerbations with the same start date and end date will be counted as one exacerbation for the purposes of calculating the number and duration of exacerbations for a subject. In the case that one or more exacerbations are recorded as starting or ending during another exacerbation, these will be counted as one exacerbation, using the earliest exacerbation start date and the latest exacerbation stop date to calculate duration.

Additional systemic corticosteroid treatments, ER or UC visits requiring use of systemic corticosteroids, or inpatient hospitalisation due to asthma occurring during an exacerbation will not be 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 will be counted as one exacerbation.

For on-treatment analyses the time at risk during which an exacerbation will be included is defined in Section 2.1.5.

For planned treatment analyses, the time at risk will be defined as follows:

If the subject attended Visit 18/EOT Week 48 (expected to be the majority of subjects), then:

Time at risk (days) = [earliest (Date of Visit 18, date of last exacerbation assessment status from the eCRF) – date of randomisation] + 1.

The date of Visit 18 will be used irrespective of how late this may have occurred in relation to the protocol schedule.

Otherwise, if no Visit 18/EOT Week 48 is available for a subject:

Time at risk (days) = [earliest (randomisation date + 336 days + 5 days; date of last exacerbation assessment during planned treatment) – date of randomisation] + 1,

where:

Date of last exacerbation assessment during planned treatment = Latest of:

1. *the date of last assessment of exacerbation status from the eCRF,*

2. *the date of death.*

The number of days the subject experiences a protocol defined exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the time at risk defined above for the primary analysis. For example, if a subject has a single exacerbation which lasts 4 days then 7 + 4 =11 days will be subtracted from the time at risk.

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 subject remained in the study with incomplete follow-up options after early discontinuation of IP.

For the main analysis (planned treatment), exacerbations that occur after a subject has discontinued IP but before the end of the time at risk will still be accounted when deriving the total number of exacerbations. Likewise, the time at risk will reflect the time at risk regardless of whether the subject is still on IP or not.

Any exacerbations that starts within the time at risk but ends after this time point will be 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 will not be included in analyses.

3.2.3 Additional endpoints supporting key secondary endpoint

3.2.3.1 Rate of asthma exacerbation associated with an ER visit or hospitalisation

To assess the effect of tezepelumab on other endpoints associated with asthma exacerbations, an annualised rate of exacerbations associated with emergency room visit or hospitalisation will be chosen as a secondary endpoint (a subset of the primary endpoint defined in Section 3.2.2.1, specifically the 2nd and 3rd bullets only).

Note that the key secondary endpoint does not consider adjudicated outcomes at all in the definition given in Section 3.2.2.1.

Another supporting endpoint will also be defined, in which exacerbations associated with hospitalisations and ER visits that are adjudicated not to be asthma related are removed, 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 3.2.2.1. Any events which are adjudicated with an "undetermined" outcome will be 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.

3.2.3.2 Time to first asthma exacerbation

Time (in days) from randomisation to the first asthma exacerbation will be used as a supportive variable to the key secondary variable, described in Section 3.2.2.1, and is calculated as follows:

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

Subjects without an exacerbation will be censored on the date of last exacerbation assessment, as defined in Section 3.2.1.

3.2.3.3 Time to first asthma exacerbation leading to ER visitor hospitalisation

Time (in days) from randomisation to the first asthma exacerbation leading to ER visit or hospitalisation will be used as a supportive variable to the key secondary variable, described in Section 3.2.2.1, and is calculated as follows:

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

Subjects without an exacerbation leading to ER visit or hospitalisation will be censored on the date of last exacerbation assessment, as defined in Section 3.2.1.

3.2.3.4 Proportion of subjects who did not experience an asthma exacerbation over 48 weeks

The proportion of subjects who did not experience an asthma exacerbation during the 48-week planned treatment period will be a supportive variable to the secondary variable described in Section 3.2.2.1. A subject will be considered to have completed the planned treatment period, if the planned treatment period is greater than 331 days (Day 336 minus 5, to account for visit windowing).

- Subjects who had no asthma exacerbations during the planned treatment period and who completed the planned treatment period (to Week 48) will be defined as exacerbation free/successful outcome [a].
- Subjects who did not complete the planned treatment period will be defined as not having a successful outcome for this endpoint [b] [c].
- Subjects who completed the planned treatment period and had an asthma exacerbation be defined as not having a successful outcome for this endpoint [d].

	No exacerbation	**Exacerbation**
Completed planned treatment period	[a] Exacerbation free/successful outcome	[d] No successful outcome
Did not complete treatment period	[b] No successful outcome	[c] No successful outcome

The proportion of subjects who did not experience an asthma exacerbation during the 48-week planned treatment period will be calculated for each treatment group as:

Number of subject's exacerbation free [a] / number of subjects in treatment group.

3.2.4 Other secondary endpoints

3.2.4.1 Proportion of subjects with 100% reduction from baseline in daily OCS dose at Week 48

For each treatment group, the number of subjects with a final daily OCS dose of 0 mg will be calculated. The proportion of such subjects will be calculated for each treatment group as:

Number of subjects with final daily OCS dose = 0 mg / number of subjects in treatment group

Final OCS dose is as described in Section 3.2.1.1.

3.2.4.2 Proportion of subjects with a daily OCS dose of ≤5.0 mg at Week 48

For each treatment group, the number of subjects with final daily OCS dose ≤5.0 mg will be calculated. The proportion of such subjects will be calculated for each treatment group as:

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

Final OCS dose is as described in Section 3.2.1.1.

Additionally, for each treatment group, the number of subjects with final daily OCS dose ≤5.0 mg and unable to reduce to 0 mg due to adrenal insufficiency will also be calculated.

3.2.4.3 Proportion of subjects with ≥50% reduction from baseline in daily OCS dose at Week 48

For each subject, if the final daily OCS dose calculated in Section 3.2.1.1 results in a value of -50% or less (more negative), that subject will be classified as having at least a 50% reduction in final daily OCS dose.

The proportion of such subjects will be calculated for each treatment group as:

Number of subjects with ≥50% reduction / number of subjects in treatment group

Final OCS dose is as described in Section 3.2.1.1.

3.2.4.4 Change from baseline in pre-BD FEV_1

Pre-BD FEV_1 will be determined by spirometry at the clinic visit. Change from baseline is obtained as an absolute difference between Week 48 measure and the baseline value as defined in Section 3.1.1. Changes from baseline at other post-baseline time points will be calculated similarly.

Only those spirometry tracings determined to be acceptable or borderline will be used. The best (highest) FEV_1 will be derived from the available individual acceptable or borderline FEV_1 measurements at each visit.

3.2.4.5 Change from baseline in weekly mean daily Asthma Symptom Diary score

Asthma symptoms during night-time and daytime will be recorded by the subject each morning and evening in the Asthma Symptom Diary (ASD). Symptoms will be recorded using a scale 0-4, 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 will be calculated separately.

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

Weekly mean scores and changes from baseline for daytime, night-time, daily scores and individual items will also be calculated. Weekly mean scores for baseline are defined in Section 3.1.1. For the Week 1 mean post-baseline, the week will start with the evening measurement on the day of randomisation and will end 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 will be missing. Weekly mean scores for all subsequent weeks will be defined similarly, with the same rule for handling missing days.

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

Change from baseline in weekly mean individual ASD items

Individual symptom scores within the ASD will be derived for each subject 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).

Weekly means will be calculated similarly to those specified above.

Another variable based on 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 $\leq$ -0.5
  - Non-responder: Change from baseline in weekly mean ASD score > -0.5.

In the above, no imputations will be performed for missing values.

3.2.4.6 Rescue medication use

The number of rescue medication inhalations and nebulizer treatments taken will be recorded by the subject in the eDiary twice daily. Daytime use is recorded in the evening and night-time use is recorded in the morning. Inhaler usage will be reported as the number of puffs in a given period whereas nebulizer use will be reported as the number of times.

The number of inhalations of rescue medication and nebulizer treatments captured in the eDiary each day will be calculated per subject. If a subject is missing a value for either nighttime or daytime rescue medication on a given day (evening followed by morning), then the total rescue medication use for that day will be set to missing.

The daily rescue medication use will be 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].

Weekly mean of the daily rescue medication use for baseline is defined in Section 3.1.1. Weekly mean scores for post-baseline weeks are similar to those for ASD in Section 3.2.4.5, with the same rule for handling missing days.

Change from baseline in the weekly mean of the daily rescue medication use will be calculated at each post-baseline week.

3.2.4.7 Home-based peak expiratory flow

Change from baseline in weekly mean morning and evening peak expiratory flow (PEF) will be calculated separately.

Home PEF testing will be performed by the subject 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). Subjects 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 will be derived from the available individual PEF measurements on each day in the morning and evening respectively.

For weekly means derived from home-based PEF, baseline is defined in Section 3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 3.2.4.5.

3.2.4.8 Night-time awakenings that required rescue medication

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 3.1.1. Weekly mean scores for post-baseline weeks are similar to those for ASD in Section 3.2.4.5, with the same rule for handling missing days.

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 will be calculated at each post-baseline week.

3.2.4.9 Total daily asthma symptom score

The total daily 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 will be recorded by the subject each morning and evening in the eDiary. Symptoms will be recorded using a scale 0-3, where 0 indicates no asthma symptoms. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning) and total daily score will be calculated and presented separately.

The total daily asthma symptom score will be calculated by taking the sum of the daytime score recorded in the evening and the night-time score recorded the following morning. If a subject 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 will be set to missing.

For weekly mean scores derived from subject eDiary, baseline is defined in Section 3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 3.2.4.5.

3.2.4.10 Change from baseline in ACQ-6 score

The ACQ-6 questionnaire includes questions on:

1. Awakening at night by symptoms
2. Limitations of normal daily activities
3. Waking in the morning with symptoms
4. Dyspnoea
5. Wheeze
6. 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 ACQ-6 score is computed as the unweighted mean of the responses to the 6 questions. If response to any of the questions is missing, the ACQ-6 will be missing.

The endpoint for the ACQ-6 will be the change in unweighted mean of ACQ-6 score from baseline at Week 48, where baseline is as defined in Section 3.1.1. Change in mean score from baseline at other post-baseline time points will be calculated similarly.

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

1. 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
2. ACQ-6 response (Improved/No Change/Deterioration):
   - Improvement: Change from baseline ACQ-6 score ≤ -0.5
   - No change: -0.5 < Change from baseline ACQ-6 score < 0.5
   - Deterioration: Change from baseline ACQ-6 score ≥ 0.5
3. Subject's asthma control as measured by ACQ-6 score:
   - Well controlled: ACQ-6 score ≤ 0.75
   - Partly controlled: 0.75 < ACQ-6 score < 1.5
   - Not well controlled: ACQ-6 score ≥ 1.5.

In the above, no imputations will be performed for missing values.

3.2.4.11 Change from baseline in AQLQ(S)+12 total score

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

The total score is calculated as the mean response to all questions. The 4 individual domain scores (4 domains assessing 1) symptoms, 2) activity limitations, 3) emotional function, and 4) environmental stimuli) are the means of the responses to the questions in each of the domains. The following are the question numbers on the AQLQ(S) +12 questionnaire relating to each domain:

Table 4 AQLQ(S)+12 domains

Domain	AQLQ(S)+12 question number
Symptoms	6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30

Domain	AQLQ(S)+12 question number
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 total score will be missing. If response to a question within a domain is missing, the score for that domain will be missing.

The endpoint for the AQLQ(S) +12 will be the change in total score from baseline at Week 48. Change from baseline in each domain will also be calculated. The definition of baseline is given in Section 3.1.1. Changes from baseline at other post-baseline time points will be calculated similarly.

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

1. 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
2. AQLQ(S)+12 response (Improved/No Change/Deterioration):
   - Improvement: Change from baseline AQLQ(S)+12 total score ≥ 0.5
   - No change: $-0.5 <$ Change from baseline AQLQ(S)+12 total score < 0.5
   - Deterioration: Change from baseline AQLQ(S)+12 total score ≤ -0.5.

In the above, no imputations will be performed for missing values.

3.2.4.12 EQ-5D-5L score

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 subject will be 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 subject will be asked to rate current health status on a scale of 0 - 100, with 0 being the worst imaginable health state.

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

The change from baseline in VAS, health state valuation index and the 5 dimensions above will be calculated for each post-baseline time point.

3.2.4.13 Health resource utilisation

Health care resource utilisation due to asthma will be recorded in the "Asthma-Related Events since Previous Visit" module of the eCRF.

The number of times (or days, as appropriate) will be calculated for each subject for the following variables at baseline, up to Week 48, and up to Week 60:

- 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

The number of times (or days) up to Week 48 (or up to Week 60) per subject will be determined as:

Sum of 'total number of times (or days)' as entered on the eCRF page from baseline up to Week 48 (or up to Week 60).

3.2.4.14 Work productivity and activity impairment

The WPAI+CIQ questionnaire is a 10-item questionnaire that assesses productivity and activity impairment over the previous week.

There are a maximum of 10 questions and a minimum of 3 questions that will be completed by subjects as follows:

1. Currently employed (yes/no)
2. Hours missed work due to health problems
3. Hours missed work due to other reasons
4. Hours actually worked
5. Degree health affected productivity while working (0-10 scale, with 0 meaning no effect)
6. Attends class in an academic setting (yes/no)
7. Hours missed class due to health problems
8. Hours actually attended class
9. Degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)
10. Degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

If the answer to question 1 'Currently employed' is 'No', then the subject should skip to question 6. If the answer to question 6 'Currently attend classes' is 'No', then the subject should skip to question 10. (Note: if the answer to question 1 'Currently employed' is 'Yes'

then subjects will be assumed not to be in school and will not be able to answer questions 6 to 9.)

The WPAI+CIQ provide 4 scores:

- Absenteeism (work or class time missed)
- Presenteeism (impairment at work or class/reduced on-the-job effectiveness)
- Work productivity loss (overall work or class impairment/absenteeism plus presenteeism)
- Activity impairment

WPAI+CIQ outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

For each time point at which the WPAI+CIQ is administered, the following descriptive statistics (if applicable) (n, total number of hours, mean per subject, standard deviation (SD), median, minimum and maximum) will be reported for those who are employed:

- # employed
- % of all subjects employed
- # of work hours missed due to asthma
- Absenteeism due to asthma
- Presenteeism due to asthma
- Work Productivity Loss
- Activity impairment

The following formulae will be used to calculate each of the outcome measures listed above:

- # currently employed – Yes in response to Question 1
- # of hours missed due to asthma – as responded in Question 2
- Absenteeism = Q2/(Q2+Q4)
- Presenteeism = Q5/10
- Work Productivity Loss = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]

- Activity Impairment = Q10/10

Similarly, the following will be reported for those subjects who are in school:

- # in school
- % of all subjects in school
- # of class hours missed
- Absenteeism due to asthma
- Presenteeism due to asthma
- Class Productivity Loss
- Activity impairment

The following formulae will be used to calculate each of the outcomes measures listed above:

- # in school - Yes to Question 6
- # of class hours missed due to asthma – as responded on Question 7
- Absenteeism due to asthma - Q7/(Q7+Q8)
- Presenteeism due to asthma – Q9/10
- Class Productivity Loss – Q7/(Q7+Q8) + [(1-Q7/(Q7+Q8))x(Q9/10)]
- Activity Impairment = Q10/10

In addition, activity impairment will be presented for those who are currently unemployed (i.e. not employed and not in school) and all subjects.

3.2.4.15 Biomarkers

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

- Fractional exhaled nitric oxide (clinic visit FENO)
- 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 3.1.1.

For clinic visit FENO, it is expected that one technically acceptable measurement will be performed at each relevant visit. In the event that more than one technically acceptable FENO measurement is available on the same date at the clinic, all data will be transferred, and the first available technically acceptable FENO measurement on that date will be used. Multiple FENO measurements on different dates will be handled according to the rules for unscheduled/repeat visits (see Section 3.1.6).

3.2.5 Exploratory endpoints

CCI

CCI

CCI

[redacted]

3.3.2 Adverse events – general

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

AEs will be categorised for analysis according to their onset date into the following study periods (see Section 4.2.8.1 for details regarding summarising AE data):

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

Note: For subjects entering the separate extension study, the study completion date will be the day of enrolment in the extension study.

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

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

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

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

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

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

3.3.3 Adverse events of special interest

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

3.3.4 Laboratory variables

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

Changes from baseline in continuous laboratory variables will be calculated at relevant visits as specified in Sections 3.1.1 and 0.

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

Absolute values will be compared to the relevant normal reference range, as provided by the central laboratory, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables.

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

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

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

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

3.3.5 Vital signs

Changes from baseline in vital signs (pulse rate, systolic blood pressure (BP), diastolic BP, respiratory rate, body temperature, body weight and body mass index (BMI)) will be calculated at relevant visits as specified in Sections 3.1.1 and 0.

BMI is calculated as:

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

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

Table 5 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	

3.3.6 12-lead digital ECG

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

Changes from baseline in continuous 12-lead digital ECG variables (data provided external to the eCRF) will be calculated at relevant visits as specified in Sections 3.1.1 and 0.

3.3.7 Physical examination

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

3.3.8 Medical history

If a partial diagnosis date is available only, the following rules will be used to impute a complete date (e.g. for derivation of time since diagnosis):

If both the month and the year are available, the first of the recorded month will be imputed, unless the date of birth is within the same month and year (where date of birth is available, which will not be the case in all countries). In this case, the date of birth will be imputed instead.

If only the year is available, 1st January will be imputed, unless the date of birth is within that same year (where date of birth is available). In this case, the date of birth will be imputed instead.

3.3.9 Glucocorticoid toxicity index

The glucocorticoid toxicity index (GTI) will be assessed as described by Miloslavsky et al 2016 (see Appendix 8.2 for details). The composite GTI measures change in common glucocorticoid (GC) toxicity rather than absolute GC toxicity in order to account for the

effects of prior GC therapy. See Section 8.2.6 of the CSP for more details. Note: change in blood pressure will be determined if there is a change in systolic BP or a change in diastolic BP.

The following 8 domains for the composite GTI will be calculated as described in Appendix 8.2: BMI, glucose tolerance (HbA1c), blood pressure, LDL, steroid myopathy, skin toxicity, neuropsychiatric toxicity and Infection. An overall score from these 8 domains will be calculated and will range from -35 to 410, with higher values reflecting greater toxicity.

3.4 Derivation of pharmacokinetic and immunogenicity variables

Serum samples for determination of tezepelumab concentrations and the presence of anti-drug antibodies (ADA) and neutralising antibodies (nAb) will be collected at baseline prior to first IP administration, at multiple time points before IP administration during the treatment period, and at selected timepoints in the follow-up period, according to the CSP schedule of assessments.

Samples will be used to determine tezepelumab concentrations, and to measure the presence of ADA and nAb, according to validated assays performed by a designated third-party vendor. Details of the bioanalytical methods used will be described in a separate bioanalytical report.

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

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

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

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Statistical hypotheses for confirmatory endpoints

The following two-sided hypotheses will be evaluated in this trial at the 0.05 significance level. All other hypothesis testing in this study will be considered exploratory.

Primary endpoint

H01: Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (tezepelumab/placebo) = 1

versus

H11: Cumulative odds ratio of percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control (tezepelumab/placebo) ≠ 1.

For 5 ordered categories, 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,

where the ordered categories for OCS daily dose reduction are in turn defined as:

- Category 1: 90% - 100% reduction
- Category 2: 75% - <90% reduction
- Category 3: 50% - <75% reduction
- Category 4: >0% - <50% reduction
- Category 5: no reduction or an increase.

The above hypothesis assumes that the 4 possible odds ratios between the 2 treatments as defined above are the same (this is the proportional odds assumption).

The direction of superiority of tezepelumab is indicated by an odds ratio greater than 1.

Key secondary endpoint

H02: AAER ratio over 48 weeks (tezepelumab/placebo) = 1

versus

H12: AAER ratio over 48 weeks (tezepelumab/placebo) ≠ 1

The direction of superiority of tezepelumab is indicated by a rate ratio less than 1.

4.1.2 Testing strategy for confirmatory endpoints

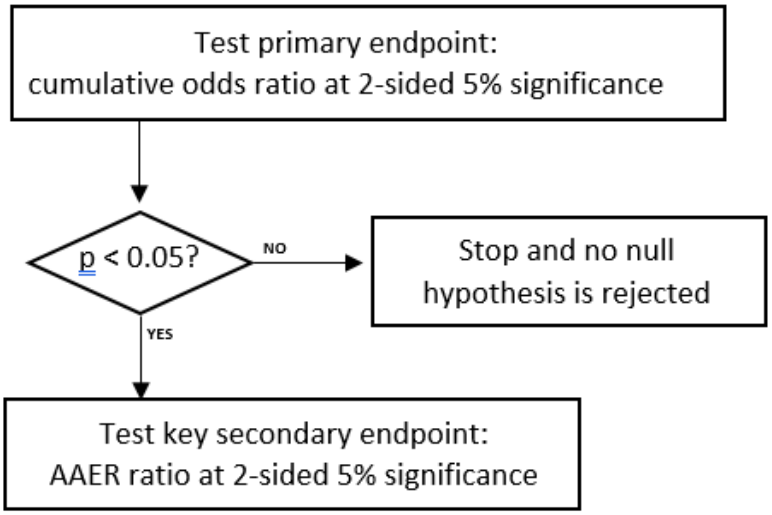
To account for multiplicity when testing the primary and the secondary endpoints, the following hierarchical testing procedure will be applied, with the hypotheses tested as defined in Section 4.1.1:

1. First the null hypothesis H01 will be tested at a 2-sided 5% significance with regard to the primary endpoint (percentage reduction category from baseline in daily OCS dose at 48 weeks whilst not losing asthma control)

2. If H01 is rejected, then the null hypothesis H02 will be tested at a 2-sided 5% significance level with regard to the key secondary endpoint (AAER ratio over 48 weeks)

See Figure 2 below.

Figure 2 Testing strategy



4.2 Analysis methods

4.2.1 Subject disposition, demography and baseline characteristics

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

Disposition summaries will also include the number and percentage of randomised subjects who subsequently participated in the planned extension study.

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

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

Demographic data such as age, gender, and race will be summarised by treatment group for the FAS. Stratification factors recorded at randomisation by the IXRS will be summarised by treatment for the FAS. All subgroups as defined in Section 3.1.8 will be summarised by treatment group for the FAS.

Various baseline characteristics will also be summarised by treatment for the FAS. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, FEV_1 (pre and post-BD) and FEV_1 reversibility, FEV_1 %predicted, $FEF_{25-75\%}$ (pre and post-BD), asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, number of asthma exacerbations requiring hospitalisations in the previous 12 months, AQLQ(S) +12 and ACQ-6. Baseline biomarker variables (FENO, eosinophils and IgE) will also be summarised by treatment for the FAS.

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

Important protocol deviations will be summarised by treatment for the FAS.

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

Additional summaries assessing the impact of the COVID-19 pandemic will be provided as described in Appendix 8.4.

4.2.2 Prior and concomitant medication

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented by treatment for the FAS. Separate tables will be presented for all medications received during each of the following periods as defined in Section 3.1.7: Prior, Concomitant (on-treatment), Concomitant (post-treatment). The number and percentage of subjects receiving systemic corticosteroids during the on-treatment period will be summarised by route of administration.

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose categories (medium/high) of ICS

medications. The number of subjects using other maintenance asthma medications at baseline will also be summarised. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per subject from the first day of IP up to Week 48 will also be summarised.

A summary of the OCS medication at study entry and baseline total daily dose will be produced. In addition, a summary of the OCS total dose at study entry to optimized baseline OCS dose will be produced. The number of subjects with OCS dose titrations during the OCS optimization period will also be summarised by visit.

A separate table will be presented for subjects who took disallowed concomitant medications.

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

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

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

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

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

4.2.3 Exposure and compliance

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

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

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

Compliance with the regularly scheduled ICS/LABA asthma inhaler as recorded in the daily diary will be summarised by each weekly period and treatment group, together with the compliance of the use of the daily diary. In addition, compliance with OCS dosing will also be presented in both the optimisation and planned treatment period.

Additional summaries assessing the impact of the COVID-19 pandemic will be provided as described in Appendix 8.4.

4.2.4 Primary endpoint

4.2.4.1 Primary analysis

The primary analysis of the primary efficacy endpoint will quantify the effect of the initially randomised treatment, regardless of the treatments that subjects actually received. Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 48-week period even after premature discontinuation of IP. This analysis will therefore include all available data after treatment discontinuation for subjects who continue to attend monthly visits either at site or by telephone.

The primary endpoint is the percentage reduction from baseline in final daily OCS dose at 48 weeks whilst not losing asthma control (as per Table 10 in the CSP), by defined categories, as described in Section 3.2.1.1.

The primary endpoint in the tezepelumab group will be compared to that in the placebo group using a proportional odds (ordinal logistic regression) model. This model will be used to perform the statistical test specified in Section 4.1.1, and to estimate the treatment effect and its 95% confidence interval. The response variable in the model will be the ordered category number (1-5) at Week 48 as defined in Section 4.1.1. Treatment and region will be included as factors in this model. Baseline OCS dose will also be included in the model as a continuous (linear) covariate. The validity of the proportional odds assumption across the categories of the response variable for the 3 factors fitted in the model will assessed by plotting empirical logits for each predictor separately. A score test statistic will also be calculated, but as it is known to be liberal (Peterson et al 1990), it will be interpreted with caution, and will be 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 or baseline OCS dose across the response, then a partial proportional odds model will be fitted, using the UNEQUALSLOPES option within SAS, to allow different effects across the categorical response for factors shown to be non-proportional. If the proportional odds assumption is not satisfied due to non-proportional effects of treatment across the response, then results will be presented from the proportional odds model, but results of the analysis will be confirmed using a Wilcoxon rank sum test stratified by region (van Elteren test) as described in Section 4.2.4.4.

Frequency tables of the number and proportion of subjects in each of the response (dose reduction) categories will be presented and a histogram of the proportion of subjects in each of the categories will also be presented. Cumulative responder (percentage reduction) plots will be presented to aid interpretation of the primary analysis. For this plot, all subjects with increase from baseline will be presented as having 0% reduction (i.e assumed to be a non-responder).

Additional analysis assessing the impact of the COVID-19 pandemic will be conducted as described in Appendix 8.4.

4.2.4.2 Sensitivity analyses

Controlled imputation

To examine the sensitivity of the results of the primary analysis for the treatment policy estimands to departures from the underlying assumptions about missing data, controlled multiple imputation analyses will be performed which allows for different underlying assumptions to be used.

The pattern mixture model analyses described below will only be performed if it is considered that the amount of missing data may impact interpretation of the primary endpoint. This will be reviewed at the final BDR.

Multiple Imputation methods – Pattern Mixture Models

The first proposed sensitivity analysis adopts multiple imputation with pattern mixture models. Imputation of missing OCS dose at each visit up to and including Week 48 (EOT) will be done in two steps:

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

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

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

- **MAR**: Missing data in each arm will be imputed assuming the distribution within that treatment group

- **Missing Not At Random (MNAR)/Dropout Reason-based Multiple Imputation (DRMI):** Missing data will be imputed differently depending on the reason for the dropout. Missing data for subjects in the tezepelumab arm who dropped out for a treatment-related reason will be imputed assuming the subject'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 subjects will be imputed assuming MAR.

Subjects with missing baseline data will be excluded from these analyses.

Step (i): In Step 1. above, a single Markov chain will be used with a non-informative (Jeffreys) prior distribution. The first 200 iterations will be 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 will be used between imputations to ensure independence between imputations

("thinning"). Convergence of the MCMC algorithm will be assessed. Non-monotone missing data are expected to be relatively infrequent.

Step (ii): The sequential monotone regression method in Step 2. 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 value is imputed at any time, it will be replaced with a zero value.

MNAR/DRMI

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

To impute missing values at time *t* for subjects in the tezepelumab arm who withdrew from the study for reasons unrelated to treatment and for all placebo subjects, the imputations are performed assuming MAR. It means that an imputation model uses subjects who had observed data at time *t* from the respective treatment group.

The following table shows how, for tezepelumab subjects who withdrew from study, each possible reason for IP discontinuation will be handled in the multiple imputation analyses described above. The rules in the table will be applied irrespective of the length of time between discontinuing IP and withdrawing from study (noting that the treatment policy strategy is used for these sensitivity analyses).

Table 6 Treatment arms for imputation of tezepelumab subjects under DRMI

Reasons for withdrawing from study	Reason for discontinuation of IP	DRMI
Death		Placebo
Site terminated by sponsor		Tezepelumab
Study terminated by sponsor		Tezepelumab
Loss to follow-up	Death	Placebo
Withdrawal by	Adverse event	Placebo

Reasons for withdrawing from study	Reason for discontinuation of IP	DRMI
Subject Other	Development of study-specific discontinuation criteria	Placebo
	Severe non-compliance to protocol	Placebo
	Subject lost to follow-up	Placebo by default (pending blinded review of any further information)
	Subject decision	Placebo by default (pending blinded review of any further information)
	Other	Placebo by default (pending blinded review of any further information)

A blinded review of subjects who withdrew from study and discontinued IP for reasons of "Subject lost to follow-up", "Subject decision" or "Other" will be performed by the study team prior to primary database lock. A listing of these subjects and the assumptions made under DRMI will be 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 subject.

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

The imputation model will use the OCS dose at the visit as the response variable and include the following predictors: the covariates incorporated in the primary statistical model, including treatment, region and baseline OCS dose, and the OCS dose at all prior (post-baseline) visits.

For each of the imputed datasets, the final daily OCS dose will be derived as described in Table 2 for subjects who prematurely discontinued IP following option 1 or 2, and who did not prematurely discontinued IP. The categorised percent change from baseline at Week 48 will be calculated as described in Section 3.2.1.1. The analysis of each of these imputed datasets will be as described for the primary analysis in Section 4.2.4.1. The results from the analysis of each imputed datasets will then be 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.

Tipping point analysis

A tipping point analysis will be performed for the primary endpoints, using similar multiple imputation methodology to examine the impact of varying the rate parameter for missing data in subjects who withdrew from the study or discontinued IP following option 3.

In this analysis, various degrees of improvement in the placebo group δ_P after withdrawal, and various degrees of worsening in the tezepelumab group δ_T after withdrawal, will be simultaneously explored.

Placebo subjects who withdrew from the study (irrespective of reason for discontinuing IP) or discontinued IP following option 3 will have their first monotone imputed value improved by δ_P. This results in a one-time shift towards a better value in the outcomes of placebo subjects that withdrew from the study or discontinued IP following option 3 after a given visit.

Tezepelumab subjects who withdrew from the study (irrespective of reason for discontinuing IP) or discontinued IP following option 3 will have their first monotone imputed value worsened by δ_T. This results in a one-time shift towards a worse value in the outcomes of tezepelumab subjects that withdrew from the study or discontinued IP following option 3 after a given visit.

Tipping points are defined as the range of smallest values (δ_P, δ_T) which would result in a change of conclusion, the latter being assessed according to the nominal statistical significance levels applied in Section 4.1.2.

Step (i) will first be applied to the non-monotone missing values, exactly as specified above for controlled imputation.

For step (ii), the sequential monotone regression method will also be applied. To impute missing values at time t for subjects in the placebo arm, an imputation model which uses placebo subjects who had observed data at time t will be used, and the one-time improvement δ_P applied to this. To impute missing values at time t for subjects in the tezepelumab arm, an imputation model which uses tezepelumab subjects who had observed data at time t will be used, and the one-time worsening δ_T applied to this. In other words, imputation will be performed within each treatment arm, and therefore (δ_P, δ_T) = (0, 0) corresponds to the MAR analysis. If a negative value is imputed at time t, then it will be replaced with a zero value.

Deltas for OCS dose are defined as follows:

- δ_P will be varied from 0 to -15 mg in increments of 5 mg,
- δ_T will be varied from 0 to 15 mg in increments of 5 mg.

If a tipping point was observed with analysis using 5 mg increments, smaller increments (e.g. 2.5 mg or 1.5 mg) will then be explored in the relevant range to determine the tipping point more precisely.

Single Imputation method – Average Dose

Where a subject withdraws from the study or discontinues IP and choses option 3 at any point after their baseline assessment and before their Week 48 assessment, the final OCS dose will be imputed to be the average daily dose that a subject was taking in the 14 days prior to their discontinuation from IP or withdrawal from the study (discontinuation from IP, if both apply). The 14 days used for this calculation should not include days where the subject received a temporary burst of systemic corticosteroids. This method will be conservative potentially for subjects who withdraw at an early stage from the study, but who may have later seen a treatment benefit. Analysis of the primary variable (categorised percentage reduction from baseline in final daily OCS dose at 48 weeks) will be repeated using this imputation. Analyses will be as described in Section 4.2.4.1.

4.2.4.3 Additional sensitivity analysis

Systemic corticosteroids (SCS) for non-asthma reasons
SCS for non-asthma reasons will be identified as medications recorded in the SYSTCORT eCRF page with a therapy reason of "Non-asthma condition" and "Other" (excluding adrenal insufficiency). The number and percentage of subjects using SCS for non-asthma reasons during the planned treatment period will be summarised by treatment group. In addition, the number and percentage will be provided for subgroups of subjects 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 subject during the planned treatment period will also be summarised.

An exploratory analysis of the final OCS dose including oral systemic corticosteroids used for reasons other than asthma at Week 48 may be performed as described for the primary analysis in Section 4.2.4.1.

4.2.4.4 Supplementary analyses

Analysis of primary endpoint using on-treatment data
The analysis specified in Section 4.2.4.1 will be repeated using on-treatment data only, where the definition of on-treatment is given in Section 2.1.5. The final daily OCS dose for subjects withdrawing from the study or prematurely discontinuing IP (regardless of chosen option) due to reason other than COVID-19 will be the last reported OCS dose received by subject when asthma stability was verified, at the time of IP discontinuation, increased by 1 dose level, as described in Table 2 and Table 3 in Section 3.2.1.1. If the subject withdrew from the study or prematurely discontinued IP due to COVID-19, then the last stable dose will not be increased by 1 dose level.

Analysis of primary endpoint using van Elteren test
As further support to the primary analysis, the categorised actual percentage reduction in daily OCS dose at Week 48, as described in 3.2.1.1, will be summarised descriptively and compared between treatments using a Wilcoxon rank sum test stratified by region (van Elteren test).

Percentage reduction from baseline in daily OCS dose

The percent reduction from baseline in daily OCS dose while not losing asthma control at Week 48, described in 3.2.1.1, will be compared between treatment groups using a Wilcoxon rank sum test sum test stratified by region (van Elteren test). The p-value will be presented.

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

The median percentage reduction from baseline in daily OCS dose in two treatment groups with 95% CIs will be displayed graphically over time. Moreover, the mean (±2SD) percentage reduction from baseline in daily OCS dose in two treatment arms will also be presented over time.

4.2.4.5 Subgroup analyses

To explore the treatment effect across categorical baseline or demographic variables as detailed in Section 3.1.8, a similar model will be 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 will be tabulated and also summarised graphically using a forest plot. A p-value for the treatment by subgroup interaction will not be presented for each of these models due to the various difficulties in interpretation.

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

4.2.5 Key secondary endpoint

4.2.5.1 Main analysis

The main analysis of the key secondary endpoint (AAER over 48 weeks) will quantify the effect of the initially randomised treatment, regardless of the treatments that subjects actually received. This analysis will therefore include all available data after treatment discontinuation until the end of the planned treatment period. Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 48-week period even after premature discontinuation of IP. Consequently, subjects lost to follow-up, subjects who die and subjects who withdraw their consent should be the only source of missing information for the primary analysis.

Missing data from early study withdrawal will be modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data are missing at random (MAR).

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. This model will be used to estimate the rate ratio and its 95% confidence interval. The response variable in the model will be the number of asthma exacerbations experienced by a subject over the 48-week planned treatment period (or shorter duration if not followed up for the full 48 weeks). Treatment, region and history of exacerbations (≤2 or >2 in previous 12 months) will be included as factors in this model. The logarithm of the time at risk (in years) for exacerbation in the study will be used as an offset variable in the model, to adjust for subjects having different follow-up times during which the events occur. Time during an exacerbation and the 7 days following an exacerbation in which a new exacerbation cannot occur, will not be included in the calculation of time at risk for exacerbation. For further details on the key secondary endpoint derivation, see Section 3.2.2.1.

Descriptive summaries of the asthma exacerbations will also be presented. Unadjusted exacerbation rates will be summarised using an approach weighted by subject's time at risk (i.e. the total number of exacerbations for each treatment divided by the total time at risk for that treatment).

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

Additional analysis assessing the impact of the COVID-19 pandemic will be conducted as described in Appendix 8.4.

4.2.5.2 Sensitivity analysis

Controlled imputation

To examine the sensitivity of the results of the key secondary analysis for the treatment policy estimands to departures from the underlying assumptions about missing data, controlled multiple imputation analyses will be performed which allows for different underlying assumptions to be used.

An underlying negative binomial stochastic process for the number of exacerbations will be assumed and post-study withdrawal counts will be imputed conditional upon the observed number of events prior to the withdrawal under both MAR and MNAR/DRMI assumptions respectively:

- MAR: Missing counts in each arm will be imputed assuming the estimated event rate within that treatment group.

- MNAR/DRMI: Missing counts will be imputed differently depending on the reason for dropout.

  Missing counts for subjects in the tezepelumab arm who dropped out for a treatment-related reason will be imputed based on the estimated event rate in the placebo arm (the "copy reference" approach), whereas the remaining subjects who dropped out will be

imputed assuming MAR. Table 6 shows how tezepelumab subjects withdrawing from study will be handled in the DRMI analyses described above. The rules in the table will be applied irrespective of the length of time between discontinuing IP and withdrawing from study (noting that the treatment policy strategy is used for these sensitivity analyses).

The methodology used for sensitivity analysis is described in more detail in Keene et al 2014. The steps for carrying out multiple imputation are outlined below.

Step 1: Fitting a negative binomial model to the observed data

A negative binomial regression model will be fitted to the observed exacerbation data with treatment group, region, and history of exacerbations included as covariates. The logarithm of the time at risk (in years) for exacerbation will be used as an offset variable in the model.

Step 2: Drawing samples from the posterior distribution

The negative binomial distribution is conventionally defined as the probability distribution of the number of successes Y before k failures are seen in a series of independent Bernoulli trials with probability p of success and (1-p) of failure.

The posterior distribution for parameter k and coefficients β will be created as a product of non-informative prior and the likelihood from the model in Step 1. A uniform prior distribution will be assumed for the regression coefficients. A Gamma (10^{-4}, 10^{-4}) will be assumed for 1/k.

With the use of Markov Chain Monte Carlo (MCMC) method, 100 samples of k and β will be drawn from their posterior distribution. Convergence of the MCMC algorithm will be assessed.

A random seed of 991511 will be used. The first 2000 iterations will be 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 will be used between imputations to ensure independence between imputations ("thinning").

Step 3: Imputing missing data

For a subject who withdrew from the study early, let Y_1 denote the number of events prior to withdrawal (over time t_1), and let Y_2 denote the number of unobserved events after withdrawal until the end of the study's planned treatment period (over time t_2). For a subject who completes the planned treatment period, Y_1 denotes the number of events prior to completion (over time t_1). Using the formula in Keene et al 2014, the unobserved events Y_2 will be imputed from a negative binomial distribution with parameters k* and p*, where:

- $k^* = k + Y_1$
- $p^* = (k + \varphi_1) / (k + \varphi_1 + \varphi_2)$

- φ_1 is the expected number of events prior to withdrawal
- φ_2 is the expected number of events after withdrawal.

Thus, Y_1+Y_2 gives the number of exacerbations (observed and imputed) over the planned treatment period, $t_1+ t_2$. A random seed of 112358 will be used for the imputation.

The parameters φ_1 and φ_2 will be derived for each set of β and k parameters sampled in Step 2 under 2 different missing data scenarios, MAR and DRMI.

Step 4: Multiple imputation algorithm

For each scenario detailed in Step 3, the algorithm for implementing multiple imputation is:

i. Select the first set of parameters ($\hat{\beta}$, $\hat{k}$) from Step 2.

ii. Impute Y_2 for each subject who discontinued from the study early, using the method outlined in Step 3.

iii. Calculate $Y_3 = Y_1+Y_2$ for all subjects, where $Y_2 = 0$ for subjects who completed the study and $Y_2 \geq 0$ for subjects who discontinued from the study early.

iv. A negative binomial regression model will be fitted using Y_3 as the response variable with treatment group, region and history of exacerbations included as covariates. For subjects completing the planned treatment period, the offset will be the logarithm of the time at risk (in years) for exacerbation. For subjects with an imputed number of exacerbations after withdrawal, the offset will be the logarithm of the study's planned treatment period, excluding the time during an observed exacerbation and the 7 days following an observed exacerbation.

v. Using the model from (iv) calculate treatment differences for the comparisons of interest.

vi. Select the next set of parameters ($\hat{\beta}$, $\hat{k}$) from Step 2 and repeat (ii) through to (v) a further 99 times.

vii. Using Rubin's formulae, summarise the sets of treatment differences in (v) to give an overall treatment difference for the comparisons of interest with 95% confidence limits. The number of events and total time-at-risk will be derived by taking the arithmetic mean of these values across the sets of data.

viii. Back-transform the estimates and 95% confidence limits to give a rate ratio and corresponding limits.

Tipping point analysis

A tipping point analysis will be performed for the primary endpoint, using similar multiple imputation methodology to examine the impact of varying the rate parameter for missing data in subjects who withdrew from the study early.

In this analysis, various degrees of improvement in the placebo group δ_P after withdrawal, and various degrees of worsening in the tezepelumab group δ_T after withdrawal, will be simultaneously explored.

Missing data will be imputed for placebo subjects who withdrew from the study (irrespective of reason for discontinuing IP or study) by multiplying the estimated placebo exacerbation rate by an improvement factor δ_P.

Missing data will be imputed for tezepelumab subjects who withdrew from the study (irrespective of reason for discontinuing IP or study) by multiplying the estimated tezepelumab exacerbation rate by a worsening factor δ_T.

Tipping points are defined as the range of smallest values (δ_P, δ_T) which would result in a change of conclusion, the latter being assessed according to the nominal statistical significance levels applied in Section 4.1.2.

Imputation will be performed within each treatment arm, and therefore (δ_P, δ_T) = (1, 1) corresponds to the MAR analysis:

- log(δ_P) will be varied from -1.5 to 0 in increments of 0.5
- log(δ_T) will be varied from 0 to 1.5 in increments of 0.5.

This corresponds to values of δ_P between 0.22 and 1, and values of δ_T between 1 and 4.5.

If a tipping point was observed with analysis using 0.5 increments, smaller increments e.g. of 0.25 may need to be explored in the relevant range to determine the tipping point more precisely.

4.2.5.3 Supplementary analyses

Analysis of key secondary endpoint using on-treatment data
The main analysis specified in Section 4.2.5.1 will be repeated using on-treatment data only, where the definition of on-treatment is given in Section 2.1.5.

4.2.5.4 Supporting analyses

Annualised rates for those exacerbations due to ER visits or hospitalisations (a subset of the key secondary endpoint defined in Section 3.2.2.1, specifically the 2nd and 3rd bullets only) will be summarised descriptively and analysed using a similar model as for the primary analysis.

Annualised exacerbation rates which consider adjudicated outcomes (see Section 3.2.3.1 for details) will also be analysed similarly to the primary analysis. This analysis will be performed for the primary endpoint and also for exacerbations due to ER visits or hospitalisations.

Time to first asthma exacerbation will be summarised using Kaplan-Meier estimates, and analysed using a Cox proportional hazards model with factors for treatment, region and history of exacerbations (<=2 or >2 in previous 12 months). This analysis will only be done on the planned treatment period (with censoring at the end of the time at risk as defined in Section 3.2.2.1 for subjects without the event).

The proportional hazards assumption will be checked. If needed, further consideration will be given to models which make less restrictive assumptions, including (but not necessarily limited to):

- Stratified proportional hazards model
- Models which assume proportional hazards over shorter piecewise time intervals.

In addition, the time to first asthma exacerbation leading to ER visits or hospitalisations will also be summarised using Kaplan-Meier estimates, and analysed using a Cox proportional hazards model as described above.

The proportion of subjects who had no asthma exacerbation during the planned treatment period, as defined in Section 3.2.3.4, will be summarised descriptively and analysed using a logistic regression model. An odds ratio and 95% confidence interval will be estimated from the logistic regression model which will include factors for treatment, region and history of exacerbations (<=2 or >2 in previous 12 months).

These supporting analyses will be performed using the treatment policy strategy only.

4.2.6 Other secondary endpoints

Analyses of all continuous secondary endpoints will be assumed a priori to meet the distributional assumptions without transformation. However, this will be evaluated during blinded data reviews, and if necessary the SAP will be updated to specify an appropriate transformation for any endpoint where this assumption is not reasonable.

Sensitivity and subgroup analyses will not be performed on exploratory endpoints.

4.2.6.1 Proportion of subjects with 100% reduction from baseline in daily OCS at Week 48

The proportion of subjects with 100% reduction from baseline in total daily OCS at Week 48 as defined in Section 3.2.4.1 will be analysed using a logistic regression model. An odds ratio and 95% confidence interval will be estimated from the logistic regression model which will include factors for treatment and region. Baseline OCS dose will also be included in the model as a continuous (linear) covariate.

Frequency tables of the number and proportion of subjects with 100% reduction will be presented.

4.2.6.2 Proportion of subjects with daily OCS dose ≤5 mg at Week 48

The proportion of subjects with a total daily OCS dose of ≤5 mg at Week 48 as defined in Section 3.2.4.2 will be analysed using a logistic regression model as described for the proportion of subjects with 100% reduction in OCS as described in Section 4.2.6.1.

Frequency tables of the number and proportion of subjects with a total daily OCS dose of ≤5 mg will be presented.

Additionally, the number and proportion of subjects with a total daily OCS dose of ≤5 mg and unable to reduce to 0 mg due to adrenal insufficiency will be presented. If there are a number of subjects with a total daily OCS dose of ≤5 mg and unable to reduce to 0 mg due to adrenal insufficiency, then a logistic regression model as described in Section 4.2.6.1 may also be performed. This analysis will be based on the proportion of subjects with a total daily OCS dose of ≤5 mg and unable to reduce to 0 mg due to adrenal insufficiency and subjects with 100% reduction in final daily OCS dose (i.e final daily OCS dose of 0 mg).

4.2.6.3 Proportion of subjects with 50% reduction from baseline in daily OCS at Week 48

The proportion of subjects with ≥50% reduction from baseline in total daily OCS at Week 48 as defined in Section 3.2.4.3 will be analysed using a logistic regression model as described for the proportion of subjects with 100% reduction in OCS as described in Section 4.2.6.1.

Frequency tables of the number and proportion of subjects with 100% reduction from baseline in total daily OCS will be presented.

4.2.6.4 Change from baseline in pre-BD FEV_1

The analysis of the change from baseline in pre-BD FEV_1 to Week 48 will quantify the effect of the initially randomised treatment at Week 48, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications, including for subjects who discontinued study treatment prior to Week 48. This analysis uses a treatment policy estimand and will therefore include all available data after treatment discontinuation until the end of the planned treatment period. Missing data will be modelled based on what was observed during the study using direct likelihood approaches, which is a valid approach under the assumption that data are missing at random (MAR).

Change from baseline in pre-BD FEV_1 in the tezepelumab group will be compared to that seen in the placebo group using a mixed model for repeated measures (MMRM) model. This model will be used to estimate the treatment effect at Week 48 and its 95% confidence interval, for each endpoint.

The response variable in the model will be change from baseline at each scheduled post-randomisation visit up to and including Week 48, and irrespective of whether the subject

remained on treatment and/or took other treatments. Treatment, visit, region and treatment by visit interaction will be included as factors in this model. Baseline pre-BD FEV_1 will also be included in the model as a continuous linear covariate. Baseline by visit interaction will not be included as a covariate in the MMRM model.

Unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same subject. To allow for the possibility that the MMRM model fails to converge with unstructured covariance, the following hierarchical approach is proposed to select a simpler covariance structure if the preceding covariance structure fails to converge: Unstructured → Heterogeneous Toeplitz → Heterogeneous First Order Autoregressive → Toeplitz → First Order Autoregressive → Compound Symmetry. Before concluding non-convergence at any step of this hierarchy, an attempt will first be made to resolve convergence problems by using different starting values of the underlying algorithm and/or adjusting singularity options. The Kenward-Roger approximation to estimating the degrees of freedom will be used for tests of fixed effects derived from the MMRM model.

Descriptive summaries will also be presented.

Adjusted means from the MMRM model above will be displayed graphically over time and used to evaluate time of onset of effect. Adjusted means will be calculated from the MMRM using the observed margins approach, in which the contribution of model factors to the estimate is weighted proportionally to the presence of these factors in the data.

4.2.6.5 Weekly mean daily Asthma Symptom Diary score

The change from baseline in the weekly mean daily ASD total score will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1, where each of the 48 weeks used for weekly mean calculation will replace visit in the MMRM model specification. Included in the model will also be the baseline weekly mean daily ASD score.

The change from baseline in weekly mean daytime and night-time ASD scores, as well as change from baseline in weekly mean individual ASD symptom scores will be analysed using a similar MMRM models described above. Baseline weekly mean daily ASD score will be replaced by baseline daytime ASD score, night-time ASD score, or appropriate weekly mean individual ASD scores. Descriptive summaries will also be presented including change from baseline in weekly mean ASD score, daytime and night-time ASD scores, and individual ASD symptom scores. The adjusted means of the change from baseline in the weekly mean daily ASD total score, weekly mean daytime and weekly mean night-time ASD scores from the MMRM model will be displayed graphically over time.

In addition, ASD responders/non-responders will be summarised descriptively and analysed using a generalised linear model for repeated measures, using a logit link function. The response variable in the model will be the binary responder status at each scheduled post-randomisation visit up to and including Week 48, irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region and treatment by visit

interaction will be included as factors in this model. Baseline of the corresponding endpoint will also be included in the model as a continuous linear covariate.

4.2.6.6 Change from baseline in weekly mean rescue medication use

The change from baseline in the weekly mean rescue medication use will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1, where each of the 48 weeks used for weekly mean calculation will replace visit in the MMRM model specification. Included in the model will also be the baseline weekly mean rescue medication use.

Descriptive summaries will also be presented.

The adjusted means of the change from baseline in the weekly mean rescue medication use from the MMRM model will be displayed graphically over time.

4.2.6.7 Change from baseline in weekly mean home PEF

The change from baseline in the weekly mean home morning and evening PEF will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1, where each of the 48 weeks used for weekly mean calculation will replace visit in the MMRM model specification. Included in the model will also be the corresponding baseline PEF value.

Descriptive summaries will also be presented.

The adjusted means of the change from baseline in the weekly mean home morning and evening PEF from the MMRM model will be displayed graphically over time.

4.2.6.8 Change from baseline in weekly mean number of night-time awakenings that required rescue medication

The change from baseline in the weekly mean number of night-time awakenings due to asthma and requiring rescue medication will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1, where each of the 48 weeks used for weekly mean calculation will replace visit in the MMRM model specification. Included in the model will also be the baseline weekly mean number of night-time awakenings.

Descriptive summaries will also be presented.

The adjusted means of the change from baseline in the weekly mean number of night-time awakenings due to asthma and requiring rescue medication from the MMRM model will be displayed graphically over time.

4.2.6.9 Change from baseline in weekly mean daily Asthma Symptom Score

The change from baseline in the weekly mean daily asthma symptom total score will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1, where each of the 48 weeks used for weekly mean calculation will replace visit in the MMRM model specification. Included in the model will also be the baseline weekly mean daily asthma symptom score.

Descriptive summaries will be presented for the weekly mean daily asthma symptom total score as well as for the weekly means for daytime and night asthma symptom scores.

The adjusted means of the change from baseline in the weekly mean daily asthma symptom total score from the MMRM model will be displayed graphically over time.

4.2.6.10 ACQ-6

The change from baseline in the unweighted mean ACQ-6 score as well in each individual item will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1. Included in the model will also be the baseline ACQ-6 value.

Descriptive summaries for unweighted mean ACQ-6 score and individual items will also be presented.

The adjusted means of the unweighted mean ACQ-6 score from the MMRM model will be displayed graphically over time.

ACQ-6 responders/non-responders will be summarised descriptively and analysed using a generalised linear model for repeated measures, using a logit link function. The response variable in the model will be the binary responder status at each scheduled post-randomisation visit up to and including Week 48, irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region and treatment by visit interaction will be included as factors in this model. Baseline ACQ-6 will also be included in the model as a continuous linear covariate.

In this model, inference will be based on generalised estimating equations (GEEs) using the method of Keene at al (2014). An unstructured working correlation matrix will be used, along with empirically corrected standard errors using the method of Liang and Zeger (1986).

Only the first (responder/non-responder) definition in Section 3.2.4.10 will be analysed using the repeated measures GEE analysis. The other categorical definitions in this section will be summarised descriptively.

Additionally, percentage of ACQ-6 responders will be displayed graphically over time.

4.2.6.11 AQLQ(S)+12

The change from baseline in the AQLQ(S)+12 total score will be analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1. Included in the model will also be the baseline AQLQ(S)+12 total score. In addition, similar models will be used for each AQLQ(S)+12 domains. Baseline AQLQ(S)+12 total score will be replaced by baseline AQLQ(S)+12 score of appropriate domain score. Descriptive summaries will also be presented for both AQLQ(S)+12 total score and 4 domains.

The adjusted means of AQLQ(S)+12 total score from the MMRM model will be displayed graphically over time.

AQLQ(S)+12 responders/non-responders will be summarised descriptively and analysed using a generalised linear model for repeated measures, using a logit link function. The response variable in the model will be the binary responder status at each scheduled post-randomisation visit up to and including Week 48, irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region and treatment by visit interaction will be included as factors in this model. Baseline AQLQ(S)+12 will also be included in the model as a continuous linear covariate.

In this model, inference will be based on generalised estimating equations (GEEs) using the method of Keene et al (2014). An unstructured working correlation matrix will be used, along with empirically corrected standard errors using a method of Liang and Zeger (1986).

Only the first (responder/non-responder) definition in Section 3.2.4.11 will be analysed using logistic regression. The other categorical definitions in these sections will be summarised descriptively.

Additionally, percentage of AQLQ(S)+12 responders will be displayed graphically over time.

4.2.6.12 EQ-5D-5L

The change from baseline in EQ-5D-5L VAS and health state valuation index will be summarised descriptively and analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1. Included in the model will also be the corresponding baseline value.

Descriptive summaries will also be provided including other EQ-5D-5L dimensions.

The adjusted means of the change from baseline in EQ-5D-5L VAS and health state valuation index from the MMRM model will be displayed graphically over time.

4.2.6.13 Health resource utilization

All HRU items defined in Section 3.2.4.13 will be summarised descriptively.

4.2.6.14 WPAI+CIQ

All WPAI+CIQ scores defined in Section 3.2.4.14 will be summarised descriptively.

4.2.6.15 Change from baseline in biomarkers

Change from baseline in biomarkers (clinic visit FENO, eosinophils (10**9/L and Cells/µL) and total serum IgE (mg/L and IU/mL)) will be summarised descriptively and analysed using the MMRM approach defined for change from baseline in pre-BD FEV_1, as described in Section 4.2.6.1. Included in the model will also be the corresponding baseline value.

Descriptive summaries will also be provided.

The adjusted means of the change from baseline in biomarkers from the MMRM model will be displayed graphically over time.

Note that eosinophil (10**9/L) and total serum IgE (mg/L) data will also be included in the summaries of laboratory data.

4.2.7 Exploratory endpoints

CCI

- CCI

4.2.8 Safety and tolerability

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

4.2.8.1 Adverse events

AEs will be summarised separately for the on-treatment and on-study periods as defined in Section 3.1.5 unless stated otherwise. All AE summaries will be presented by treatment group. AEs occurring during the screening/run-in/optimization period, or occurring post-treatment will be listed, but not summarised separately.

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

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

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

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

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

The AESI of injection site reactions will be further summarised by:

- Site of injection (arm, thigh, abdominal wall)
- Total number of doses administered (1, 2, …, 12), irrespective of timing of the injection site reaction event.

Exposure-adjusted AE summaries will be presented by SOC and PT for each of the following (on-treatment summaries only):

- All AEs
- Each AESI separately

In these summaries, the exposure-adjusted rate will be defined for each treatment as the number of subjects in that treatment group reporting the AE divided by the by extent of exposure, as defined in 3.3.1, for all subjects in that treatment group. Rates will be reported as events per 100 subject-years.

Events confirmed by the independent adjudication committee (major adverse cardiac events (MACE) and malignancies) will be summarised by treatment.

Additional summaries assessing the impact of the COVID-19 pandemic will be provided as described in Appendix 8.4.

4.2.8.2 Laboratory data

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

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

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

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

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

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

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

For urinalysis data, a shift table will be generated to present changes from baseline to maximum/last value post-baseline. All data for the on-study period will be used.

All summaries and figures will report laboratory data in SI units.

4.2.8.3 Vital signs

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

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

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

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

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

4.2.8.4 12-lead digital ECG

Continuous 12-lead digital ECG variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. These summaries will be produced for the on-study period, as defined in Section 3.1.5. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

A shift table will be produced to display the investigator assessment of normal, abnormal – not clinically significant, abnormal – clinically significant and not done between baseline and end of study. For this purpose, borderline (also recorded on the eCRF) will be grouped with normal.

A frequency table showing subjects with Frederician corrected QT (QTc) values and increases from baseline at any time during the on-study period using standard pre-specified thresholds will be produced.

4.2.8.5 Physical examination

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

4.2.8.6 Glucocorticoid toxicity index

The glucocorticoid toxicity index total score and the 8 domains, as defined in Section 3.3.9, will be summarised descriptively at each visit by treatment group. The summary statistics presented for the glucocorticoid toxicity index total score will be minimum, median, maximum, mean and SD. The 8 domains will be presented as numbers and percentages of subjects in each category within a domain. These summaries will be produced for the planned treatment period, as defined in Section 3.1.5.

4.2.9 Pharmacokinetics and immunogenicity

4.2.9.1 Analysis of pharmacokinetics

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

Serum tezepelumab concentrations will be summarised 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, 4, 12, 24, 40, 48, 60 and at the premature IP discontinuation visit, where appropriate. Data will be assigned to weeks based on the windows defined in Section 3.1.6.

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

- Only pre-dose samples at week 0.
- Only pre-dose samples at weeks 4, 12, 24 and 40 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 48.
- All samples for week 60 that were taken within the visit window defined in Section 3.1.6.

For descriptive statistics of tezepelumab concentrations:

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

- The median, minimum and maximum will also be reported.

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

If appropriate, descriptive statistics of tezepelumab concentrations over time will also be 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 4.2.9.2).

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

4.2.9.2 Analysis of immunogenicity

All analyses of immunogenicity variables will be based on the safety analysis set as defined in Section 2.1.2.

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

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

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

- Subjects with treatment boosted ADA, defined as baseline positive ADA titre that was boosted to a 4 fold or higher level following IP administration
- Subjects with treatment emergent ADA (ADA incidence): defined as the sum of treatment induced ADA and treatment boosted ADA.

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

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

Neutralizing ADA evaluations will be 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 subjects who are nAb positive at any time will be evaluated.

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

5. INTERIM ANALYSES

No interim analyses are planned in this trial.

An independent Data and Safety Monitoring Board (DSMB) will review safety data on a regular basis as set out in a DSMB charter. The data for review will be outlined in the DSMB charter. The DSMB will have access to individual treatment codes and will be able to merge these with the collected study data while the study is ongoing. The personnel involved in the clinical study at AstraZeneca will remain blinded to these analyses and will have no knowledge of the results presented to the DSMB.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The CSP specifies that in general the last measurement on or prior to the date of randomisation will serve as the baseline measurement. This is clarified in Section 3.1.1 as being with reference to the date of randomisation for efficacy variables, but date of first dose of IP with reference to safety variables (should a situation exist for any subject in which these two dates are different).

Mean daily exposure of systemic corticosteroids over 48 weeks has been included as an exploratory endpoint in the Section 3.2.5.1 but is not included as an exploratory endpoint in the protocol.

The protocol specifies that one of the exploratory objectives is to explore the effect of 210 mg tezepelumab SC Q4W on total immunoglobulin levels. Total serum IgE is included in Section

1.1.3, Other Secondary Objectives: To assess the effect of 210 mg tezepelumab SC Q4W on biomarkers, so removed from Section 1.1.5.

The number of asthma symptomatic days has been included as an exploratory endpoint in the Section 3.2.5.4 but is not included as an exploratory endpoint in the protocol.

Description of analysis of primary endpoint (categorised percentage reduction in final daily OCS dose at Week 48) using van Elteren test stratified by region has been added in the Section 4.2.4.4, but is not included in the protocol.

The protocol defines an emergency room or urgent care visit due to asthma that requires systemic corticosteroids, as one of 3 criteria for a protocol defined exacerbation. However, only information on emergency room visits and use of systemic corticosteroids is collected in the eCRF. The text in Sections 3.2.2.1, 3.2.3.1 and 3.2.3.3 has been updated to reflect this.

The protocol specifies that serum trough concentrations will be the endpoint used to evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab; we will include data from follow-up visits where appropriate, so the word 'trough' has been removed from Section 1.1.3.

The total daily asthma symptom scores, derived from the Global Asthma Symptom items assessment used for the alerts system, has been included as an exploratory endpoint in Section 3.2.4.9, but is not included as an exploratory endpoint in the protocol. The daytime and night time scores from this assessment have also been included.

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8. APPENDIX

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

8.1.1 Anaphylactic reactions

Potential anaphylactic reactions will be defined on the basis of Sampson's criteria (Sampson et al 2006). These will be identified using a modified Standardized MedDRA Query (SMQ),

with additional constraints on the timing of the AE onset date relative to the timing of the injection.

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

8.1.2 Immune complex disease (Type III hypersensitivity reactions)

Immune complex disease will be defined using a single PT of "Type III immune complex mediated reaction". Since this will already be covered by the general AE reporting by SOC/PT, separate summary tables will not be needed for this AESI.

8.1.3 Malignancy

Malignancy will be defined on the basis of an SMQ.

8.1.4 Helminth infections

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

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

8.1.5 Severe infections (as defined in the protocol)

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

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

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

8.1.6 Injection site reactions

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

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

8.1.7 Opportunistic infections

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

8.1.8 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

8.1.9 Adrenal Crisis

Adrenal crisis will be defined using a pre-specified list of high level and lower level MedDRA terms.

8.2 Glucocorticoid toxicity index

Any untoward medical occurrences captured as part of the GTI assessment should be reported as an adverse event. This includes but is not limited to any clinically significant worsening of a subject's pre-existing condition (i.e. worsening of glucose tolerance, etc.).

Eight domains and 28 items are included in the composite glucocorticoid toxicity index (GTI).

For item weights please see table below. Details for scoring each item is provided at the end of the table.

Adapted from Miloslavsky EM, Naden RP, Bijlsma JWJ, et al. Ann Rheum Dis Published Online First:29 July 2016 doi:10.1136/annrheumdis-2016-210002

The Glucocorticoid Toxicity Index (GTI)	
Composite GTI	**Item weight**
BMI	
• Improvement in BMI	–8
• No change in BMI	0
• Moderate increase in BMI	21
• Major increase in BMI	36
Glucose tolerance	
• Improvement in glucose tolerance	–8
• No change in glucose tolerance	0
• Worsening of glucose tolerance	32
• Worsening of glucose tolerance despite treatment	44
Blood pressure	

The Glucocorticoid Toxicity Index (GTI)	
Composite GTI	**Item weight**
• Improvement in blood pressure	−10
• No change in blood pressure	0
• Worsening hypertension	19
• Worsening hypertension despite treatment	44
Lipids	
• Improvement in lipids	−9
• No change in lipids	0
• Worsening hyperlipidaemia	10
• Worsening hyperlipidaemia despite treatment	30
Steroid myopathy	
• No steroid myopathy	0
• Mild steroid myopathy	9
• Moderate steroid myopathy or greater	63
Skin toxicity	
• No skin toxicity	0
• Mild skin toxicity	8
• Moderate skin toxicity or greater	26
Neuropsychiatric toxicity	
• No neuropsychiatric symptoms	0
• Mild neuropsychiatric symptoms	11
• Moderate neuropsychiatric symptoms or greater	74
Infection	
• No significant infection	0
• Oral/vaginal candidiasis or uncomplicated zoster	19
• Grade III infection or greater	93
Total	−35 to 410

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1. **Body Mass Index (BMI) (compared to baseline)**

   a. Improvement in the direction of the normal range by more than 2 BMI units (normal range = 18.5-24.9 kg/m^2)
   b. No significant change (BMI remains within +/- 2 BMI units compared with baseline) OR BMI remains within the normal range
   c. Moderate increase in BMI (increase by more than 2 but less that 5 BMI units, to above the upper limit of normal BMI [24.9 kg/m^2])
   d. Major increase in BMI (increase by at least 5 but less than 8 BMI units above normal BMI [24.9 kg/m^2])

2. **Glucose Tolerance (compared to baseline)**

   a. Improvement in glucose tolerance:
      - HbA1c declined >10% from baseline without medication increase
        OR
      - Decrease in diabetic medication without an increase in HbA1c of >10% or

HbA1c < 5.7%

b. No significant change in glucose tolerance:
   - HbA1c within 10% of baseline or HbA1c < 5.7% AND no change in medication
     OR
   - HbA1c increased to > 10% of baseline with a decrease in medication
     OR
   - HbA1c decreased by > 10% of baseline with an increase in medication

c. Worsening of glucose tolerance or medication status:
   - HbA1c > 5.7% and increased to >10% of baseline without a change in medication
     OR
   - Increase in diabetic medication with < 10% increase in HbA1c

d. Worsening of glucose tolerance despite increased treatment:
   - HbA1c > 5.7% AND increased to >10% of baseline AND an increase in diabetic medication

3. **Blood Pressure (BP) (compared to baseline)**

a. Improvement in BP:
   - Decrease in BP of >10% of baseline without medication increase, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85
     OR
   - Decrease in medication without an increase in BP of >10%, unless baseline systolic BP ≤ 120 and diastolic BP ≤ 85

b. No significant change in BP:
   - BP within 10% of baseline or systolic BP ≤ 120 and diastolic BP ≤ 85 AND no change in medication
     OR
   - Increase in either systolic or diastolic BP >10% with a decrease in medication
     OR
   - Improvement in systolic or diastolic BP of > 10% with an increase in medication

c. Worsening of hypertension:
   - Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication
     OR
   - An increase in anti-hypertensive medication accompanied by stability or no significant change in both the systolic and diastolic BP

d. Worsening of hypertension despite treatment:
   - Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg AND an increase in medication

4. **Lipid metabolism (low-density lipoprotein [LDL] compared to baseline)**

a. Improvement in lipids:
   - Decrease in LDL concentration >10% of baseline toward the target range without medication increase
     OR
   - Decrease in medication without an increase in LDL of >10% or LDL remains

within target range b. No significant change in LDL: • LDL within 10% of baseline or within the target range for patient AND no change in medication OR • Increase in LDL > 10% with a decrease in medication OR • Improvement in LDL of > 10% with an increase in medication c. Worsening of LDL or medication status: • Increase in LDL of >10% to above target range without a change in medication OR • Increase in medication with <10% change in LDL d. Worsening of LDL despite treatment: • Increase in LDL of >10% AND an increase in medication
5. **Glucocorticoid-induced myopathy** a. No steroid myopathy b. Mild steroid myopathy (weakness WITHOUT functional limitation) c. Moderate steroid myopathy (weakness WITH functional limitation) **See Steroid Myopathy definitions, below**
6. **Skin** a. No skin toxicity b. Mild skin toxicity c. Moderate skin toxicity **See Skin definitions, below**
7. **Neuropsychiatric toxicity** a. No neuropsychiatric symptoms b. Mild neuropsychiatric symptoms c. Moderate neuropsychiatric symptoms **See Neuropsychiatry definitions, below**
8. **Infection (since last assessment)** a. No significant infection b. Specific infections < Grade 3 (oral or vaginal candidiasis, uncomplicated zoster) c. Grade 3 or complicated herpes zoster **See Infection definitions, below**

Glucocorticoid-induced myopathy definitions

Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy, and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits.

Mild and moderate severity of myopathy are defined by a muscle strength of 4 on the standard Medical Research Council rating scale. A 4 means weaker than normal but greater than antigravity strength against resistance.

"Mild" is mild weakness (Grade 4) that does NOT functionally limit the patient.

"Moderate" is mild weakness (Grade 4) that does impose functional limitations on the patient enough to interfere with normal daily activities.

Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that detectable on physical examination but might not be aware of it or have any corresponding functional limitation - this would be classified as mild.

Severity of glucocorticoid toxicity in the skin

Manifestations to be considered:

• Acneiform rash	• Atrophy/striae
• Easy Bruising	• Erosions/tears/ulcerations
• Hirsutism	

Skin 6b. Mild	Skin 6c. Moderate
Acneiform rash (Grades 1-2)	Acneiform rash (Grade 3)
Easy bruising (Grade 1)	Easy bruising (Grade 2)
Hirsutism (Grade 1)	Hirsutism (Grade 2)
Atrophy/Striae (Grade 1)	Atrophy/Striae (Grade 2)
Erosions/Tears/Ulcerations (Grade 1)	Erosions/Tears/Ulcerations (Grade 2)

Skin Definitions (from National Cancer Institute Common Terminology Criteria for Adverse Events):

Acneiform rash
- Grade 1 - Papules and/or pustules covering <10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2 – Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR associated with psychosocial impact; OR limiting instrumental Activity of Daily Living (ADL)
- Grade 3 - Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; OR limiting self-care ADL; OR associated with local superinfection with oral antibiotics indicated

Easy bruising
- Grade 1 – Localized or in a dependent area
- Grade 2 - Generalized

Hirsutism - In women, increase in length, thickness or density of hair in a male distribution
- Grade 1 - Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair

- Grade 2 - Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; OR associated with psychosocial impact

Atrophy / Striae

- Grade 1 - Covering <10% BSA; OR associated with telangiectasias or changes in skin color
- Grade 2 – Covering 10 - 30% BSA; OR associated with striae or adnexal structure loss

Erosions / Tears / Ulcerations

- Grade 1 – Combined area of ulcers <1 cm; OR non-blanchable erythema of intact skin associated with warmth or erythema
- Grade 2 – Combined area of ulcers 1 - 2 cm; OR partial thickness skin loss involving skin or subcutaneous fat

Severity of neuropsychiatric glucocorticoid toxicity

Manifestations to be considered:

• Insomnia	• Cognitive Impairment
• Mania	• Depression

7b. Mild	7c. Moderate
Insomnia – (Grade 1)	Insomnia – (Grade 2)
Mania (Grade 1)	Mania (Grade 2)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)
Depression (Grade 1)	Depression (Grade 2)

Definitions of severity within the neuropsychiatric domain

Insomnia - Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening

- Grade 1: not associated with functional impairment
- Grade 2: associated with functional impairment

Mania

- Grade 1: Slightly or occasionally elevated or irritable mood and 0-1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.
- Grade 2: Frequent or moderately elevated or irritable mood and 2-3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

Cognitive impairment

- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids.
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids.

Depression

- Grade 1: Feeling slightly down or depressed and 0-2 mild or occasional addition symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.
- Grade 2: Frequent or moderate feelings of being down or depression and/or 3-4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.

Infection Definitions

No significant infection = No specific infections or serious infections, grade 3 or greater

Specific Infections – Oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement

Grade 3 – Intravenous antibiotic, antifungal, or antiviral intervention or hospitalisation indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by post-herpetic neuralgia or eye involvement

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8.3 Maintenance therapy equivalence table

Estimated daily doses for inhaled corticosteroids

Asthma Therapy	**Total Daily Dose (µg/day)**	
Inhaled Corticosteroid	**Medium**	**High**
Beclomethasone dipropionate (non HFA)	1000	>1000
Beclomethasone HFA	400	>400
Ciclesonide	320	>320
Triamcinolone acetonide	2000	>2000
Flunisolide	2000	>2000
Fluticasone furoate (e.g. Arnuity® Ellipta®)	n.a.	200
Fluticasone propionate	500	>500
Fluticasone propionate HFA	440-500	>500
Budesonide	800	>800
Mometasone furoate	440	>440
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
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 2017 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.

Estimated OCS dose therapy equivalence

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

Oral Corticosteroid	**Approximate equivalence dose**
Prednisone	10 mg
Prednisolone	10 mg

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

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

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

In order to assess the impact of the COVID-19 pandemic on the planned analyses, further additional summaries and analyses will be conducted. These are described below, with the section of the main SAP in which they relate to.

The start date of the COVID-19 pandemic is defined as 11th March 2020; the date the World Health Organisation (WHO) declared it a pandemic. Where applicable, as described below, data will be presented prior to the start of the pandemic, and during the pandemic. No post-pandemic period is defined as it is expected that the majority of subjects will have completed the study before the end date of the pandemic can be defined.

Section 2.2 Violations and Deviations

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

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

Section 4.2.1 Subject disposition, demography and baseline characteristics

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

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

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

Section 4.2.3 Exposure and Compliance

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

A summary of OCS titrations schedules impacted by COVID-19 (missed titration due to missed visit, stopped down titration due to COVID-19), will be summarised by treatment group.

Section 4.2.4.1 Additional analysis of primary endpoint

To remove any possible effect of COVID-19 pandemic outbreak (known and unknown) on the primary endpoint the analysis specified in Section 4.2.1 will be repeated including only those subjects who completed the planned treatment period prior to 11th March 2020.

Additionally, to explore the treatment effect across subjects who completed the planned treatment period prior to 11th March 2020 within subgroups defined by baseline eosinophils (<300/μL, ≥300/μL), a similar model will be fitted as for the primary analysis with additional factors including baseline eosinophil subgroups variable and its interaction with treatment. The estimate of the treatment effect and its 95% CI within each of the subgroup categories will be tabulated and also summarised graphically using a forest plot. A p-value for the treatment by subgroup interaction will not be presented for each of these models due to the various difficulties in interpretation.

Section 4.2.5.1 Additional analysis of key secondary endpoint

An additional analysis of the key secondary endpoint (AAER) will be performed based on the hypothetical scenario that the COVID-19 pandemic did not occur. This approach assumes that the response for subjects whose participation during the planned treatment period was impacted by the COVID-19 pandemic is different from those subjects who were not impacted. A hypothetical strategy will be used which will include all available data during the planned treatment period prior to 11th March 2020.

The time at risk for this analysis will be defined as follows:

If the subject attended Visit 18/EOT Week 48 (expected to be the majority of subjects), then:

Time at risk (days) = [earliest (Date of Visit 18, date of last exacerbation assessment status from the eCRF, 10th March 2020) – date of randomisation] + 1.

The date of Visit 18 will be used irrespective of how late this may have occurred in relation to the protocol schedule.

Otherwise, if no Visit 18/EOT Week 48 is available for a subject:

Time at risk (days) = [earliest (randomisation date + 336 days + 5 days; date of last exacerbation assessment during planned treatment, 10th March 2020) – date of randomisation] + 1,

where:

Date of last exacerbation assessment during planned treatment = Latest of:

1. *the date of last assessment of exacerbation status from the eCRF,*

2. *the date of death.*

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model as described in Section 4.2.5.1. Results will also be included in the forest plot for the key secondary endpoint. Descriptive statistics will also be presented.

Section 4.2.8.1 Adverse Events

The number and percentage of subjects reporting COVID-19 AEs (as defined based on the COVID-19 MedDRA terms) will be summarised by System Organ Class (SOC) and Preferred Term (PT) for the on-treatment and on-study periods.

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

For the adjudication AE summary tables, the number of subjects reported AEs that were adjudicated to be related to COVID-19 will be included. The adjudication listing will show the adjudicated relationship to COVID-19 (related, not related, undetermined, and not applicable). Not applicable will be used for AEs with an onset date prior to 01 January 2020.

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