Statistical Analysis Plan

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A Regional, Multicentre, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults with Severe Uncontrolled Asthma (DIRECTION)

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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	Annualised asthma exacerbation rate
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
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
CompEx	Composite Endpoint for Exacerbations
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Adverse Event Leading to Discontinuation of Investigational Product
DBL	Database Lock
DL	Direct Likelihood
DRMI	Dropout Reason-based Multiple Imputation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	European Quality of Life – 5 Dimensions 5 Levels Questionnaire
ER	Emergency Room
FAS	Full Analysis Set

Abbreviation or special term	Explanation
$FEF_{25-75\%}$	Forced Expiratory Flow over 25-75% of the vital capacity
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GEE	Generalised Estimating Equation
HRU	Health Resource Utilization
ICS	Inhaled Corticosteroids
IgE	Immunoglobulin E
IP	Investigational Product
IPD	Investigational Product Discontinuation
ITT	Intent-to-Treat
IXRS	Interactive Voice/Web Response System
L	Litre
LABA	Long-Acting Beta Agonist
LLOQ	Lower Limit of Quantification
LOESS	Locally Estimated Scatterplot Smoothing
MACE	Major Adverse Cardiac Events
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing Not At Random
NA	Not Applicable
nAb	Neutralizing Antibodies
NC	Not Calculable
NQ	Non-quantifiable
OCS	Oral Corticosteroids
PD	Protocol Deviation
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
PT	Preferred Term
Q4W	Every 4 Weeks
QTcF	Fridericia Corrected QT Interval

Abbreviation or special term	Explanation
REML	Restricted maximum likelihood
SABA	Short-Acting Beta Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SGRQ	St George's Respiratory Questionnaire
SMQ	Standardized MedDRA Query
SNOT-22	Sino-Nasal Outcome Test (22 item version)
SOC	System Organ Class
TBL	Total Bilirubin
UC	Urgent Care
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
VAS	Visual Analog Scale
WHO	World Health Organisation

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with CSP?	Rationale
NA	27-Dec-19	Initially approved SAP. In line with CSP version 2.0 (18-Feb-19).	NA	NA
Primary or secondary endpoints	5-Sep-22	Section 1.1.3: Removed "urgent care visit (UC)" from the outcome variable for other endpoint associated with asthma exacerbation.	Yes (CSP version 5.0, 17-May-22)	Terminology to describe emergency room (ER) and UC visits may differ between countries. All such visits have been captured as ER visits on eCRF.
Derivation of primary or secondary endpoints	5-Sep-22	Section 3.1.1: Added the baseline definitions for pharmacokinetics (PK) and immunogenicity variables.	Yes (CSP version 5.0, 17-May-22)	Provided additional clarification.
Derivation of primary or secondary endpoints	5-Sep-22	Section 3.1.1: Baseline definition clarified regarding the use of unscheduled visits in the baseline derivation and to ensure consistent approach taken for using last available measurement prior to randomisation or first dosing.	Yes (CSP version 5.0, 17-May-22)	Removed redundant text for simplification and provided additional clarification.
Derivation of primary or secondary endpoints	5-Sep-22	Section 3.1.4: Clarified "Planned treatment period" would only apply to efficacy analyses and "On-study period" would consist of "On-treatment period" and "Post-treatment/follow-up period".	NA	Provided additional clarification.
Derivation of primary or secondary endpoints	5-Sep-22	Sections 3.1.5, 4.2.9.1: Clarified the visit windows for electrocardiogram (ECG), PK and immunogenicity variables would follow the default visit windows. Provided additional rules for PK data to be included in the by-visit	NA	Provided additional clarification.

		summary and how multiple anti-drug antibodies (ADA) samples would be handled in the visit window.		
Derivation of primary or secondary endpoints	5-Sep-22	Section 3.2.1.1: Noted the definition of an exacerbation was from the CSP and clarified that ER and UC visits were captured as ER visits on the eCRF page.	Yes (CSP version 5.0, 17-May-22)	To provide clarification that the definition of an exacerbation in line with the CSP and the limitation of data collection.
Derivation of primary or secondary endpoints	5-Sep-22	Section 3.2.1.1: Updated the derivation of time at risk: allowed the date of last exacerbation assessment to be considered if Visit 17 occurred and clarified the date of last exacerbation assessment was important if Visit 17 not occur .	Yes (CSP version 5.0, 17-May-22)	To clarify that Visit 17 is not the only determinant in the derivation and the date of last exacerbation assessment is also important determinant.
Derivation of primary or secondary endpoints	5-Sep-22	Sections 3.2.3.1, 3.2.4.1, 4.2.4.4, 4.2.6: Removed “UC visit” from secondary and supportive analyses.	Yes (CSP version 5.0, 17-May-22)	Terminology to describe ER and UC visits may differ between countries. All such visits have been captured as ER visits on the eCRF page.
Derivation of primary or secondary endpoints	5-Sep-22	Section 3.2.4.1: Clarified that subjects without an exacerbation would be censored at the end of time at risk for exacerbation, instead of the date of last exacerbation assessment.	NA	Time to first exacerbation is assessed during the 52 weeks planned treatment period. However exacerbations can be collected until Week 64 per CSP.
Derivation of primary or	5-Sep-22	Section 3.2.4.1: Clarification provided for the endpoint derivation of proportion of subjects	Yes (CSP version	Provided additional clarification.

secondary endpoints		who did not experience an asthma exacerbation.	5.0, 17-May-22)	
Derivation of primary or secondary endpoints	5-Sep-22	Sections 3.4, 4.2.9.2: Replaced "Samples confirmed positive for ADA will be archived for possible testing for neutralizing antibodies (nAb)" with "Samples confirmed positive for ADA will be tested for nAb and the nAb status will be summarized by treatment group".	Yes (CSP version 5.0, 17-May-22)	To reflect nAb will be tested and analyzed.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Section 2.1.3: Updated the definition of PK analysis set: replaced "concentration from a sample collected post-dose" by "concentration from a PK blood sample collected post-first dose which is assumed not to be affected by factors such as protocol deviations (PDs)".	Yes (CSP version 5.0, 17-May-22)	Clarified that subjects and samples may be excluded from PK analysis set on the basis of PDs.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Sections 4.2.4.1, 4.2.4.4, 4.2.5.1, Appendix 8.5: Updated that not all events used "treatment policy" strategy, e.g. "while alive" apply to death. Addition of Appendix 8.5 for details regarding estimand for primary and key secondary endpoints.	NA	Added text regarding estimand per latest authority guidance.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Sections 4.2.4.2, 4.2.5.2: Additional specification provided for the imputation algorithm of missing data, the prior and posterior distributions, and the rules how tezepelumab subjects withdrawing from study handled in the dropout reason-based multiple imputation (DRMI).	NA	Provided additional clarification, for consistency of approach across tezepelumab studies, following authority guidance and recommendation.
Statistical analysis method for the primary or	5-Sep-22	Sections 4.2.4.2, 4.2.5.2: Clarified that death was not the source of missing data but the imputation	NA	Provided additional clarification.

secondary endpoints		would still be done for death for impact assessment.		
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Section 4.2.5.1: Noted that subjects selecting option 2 or 3 for follow-up would be a source of missing information for the key secondary endpoint analyses.	Yes (CSP version 5.0, 17-May-22)	Provided additional clarification.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Sections 4.2.5.1, 4.2.5.2, 4.2.5.4, 4.2.5.5, 4.2.6, 4.2.7: The model description for the change from baseline analyses changed to "a linear model for repeated measures", instead of "a mixed model for repeated measures (MMRM)".	Yes (CSP version 5.0, 17-May-22)	No changes to analyses, updated the description for clarity. MMRM is not proper description because the random effect is not assumed for subject.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Section 4.2.5.1: Updated that the first covariance structure within the hierarchy that allowed all models for individual/domain/total score would be selected for key secondary questionnaires.	NA	To ensure model consistency of questionnaires.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Section 4.2.5.1: Updated that asthma symptom diary (ASD) endpoint would not follow the default covariance structure hierarchy for key secondary endpoints.	NA	Simpler covariance structure would be selected first due to the large amount of diary data.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Section 4.2.5.2: Clarified that subjects with missing baseline data would be excluded from the sensitivity analyses for key secondary endpoints.	Yes (CSP version 5.0, 17-May-22)	Provided additional clarification.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Section 4.2.5.2: Removed tipping point analyses from the sensitivity analyses for key secondary endpoints.	NA	Due to computational complexity of tipping point analyses and controlled sequential multiple imputation analyses are considered to be

				sufficient for sensitivity analyses.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Sections 4.2.5.4, 4.2.5.5, 4.2.6, 4.2.7: Clarified that the "compound symmetry" covariance structure would be used directly after the "unstructured" covariance structure for the secondary and exploratory endpoints.	NA	Provided clarity for TFLs.
Statistical analysis method for the primary or secondary endpoints	5-Sep-22	Appendix 8.4: Addition of analyses to assess the impact of the COVID-19 pandemic.	Yes (CSP version 5.0, 17-May-22)	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Section 2.1: Clarified that randomized subjects analysis set would be used for subject listing not for disposition reporting.	Yes (CSP version 5.0, 17-May-22)	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 2.2: Categories for grouping important PDs updated.	Yes (CSP version 5.0, 17-May-22)	For consistency with the latest study non-compliance handling plan.
Data presentations	5-Sep-22	Section 2.2: Clarified that PDs will not be used to exclude subject and data in an analysis set, with the exception of the PK analysis set.	Yes (CSP version 5.0, 17-May-22)	For consistency with updated definition of PK analysis set.
Data presentations	5-Sep-22	Sections 3.1.4, 3.1.6, 3.3.2, 4.2.8.1: Updated "Post treatment period" to "Post-treatment/Follow-up period" and clarified the start date began after the on-treatment period.	NA	For consistency with programming reporting requirements and updated for clarity.
Data presentations	5-Sep-22	Section 3.1.5: Clarified that any listings produced would include all data recorded. Removed duplicate text regarding the follow-up visit.	NA	Provided additional clarification.
Data presentations	5-Sep-22	Sections 3.1.7, 4.2.1: Clarified that only frequency and percentage would be produced for subgroups	NA	Provided additional clarification.

		defined for demographic and baseline summaries.		
Data presentations	5-Sep-22	Section 3.1.7: Added more efficacy subgroup analyses for baseline eosinophils, baseline fractional exhaled nitric oxide (FENO).	NA	Additional subgroup analyses to assess efficacy across key phenotypes.
Data presentations	5-Sep-22	Section 3.1.7: Added more subgroups for baseline summary: exacerbations during medium-high dose inhaled corticosteroids (ICS) background treatment in the year before study, chronic rhinosinusitis with nasal polyps (CRSwNP), nasal polyps, nasal polyps in the 2 years before randomisation, chronic sinusitis, rhinitis status at study entry.	NA	Additional subject baseline characteristics for descriptive summary.
Data presentations	5-Sep-22	Sections 3.1.7, 4.2.4.5, 4.2.5.5: Changed age categories from adults (>65), adults (≥18 to ≤65) to adults (≥65), adults (≥18 to <65).	NA	In line with AZ standards.
Data presentations	5-Sep-22	Sections 3.1.7, 4.2.4.5, 4.2.5.5: Definition of OCS subgroup changed from OCS at study entry to OCS at baseline and added the definition of baseline.	NA	OCS at baseline is the relevant subgroup instead of OCS at study entry.
Data presentations	5-Sep-22	Sections 3.2.3.5 and 4.2.5.4: Percentage of symptomatic days will be presented instead of non-symptomatic days.	NA	Preference for reporting of this endpoint.
Data presentations	5-Sep-22	Sections 3.2.4.2, 4.2.4.5, 4.2.5.5, 4.2.6: Clarified units to be used for reporting biomarkers (FENO, eosinophils and total serum immunoglobulin E (IgE)).	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 3.2.4.3: Terminology “Asthma symptom score” changed to “Total daily asthma symptom score” and clarified that this was	NA	Provided clarity for TFLs.

		different from the daily score derived from the ASD. Clarified night-time awakenings were those that required rescue medication.		
Data presentations	5-Sep-22	Section 3.2.4.5: Addition of on-study and past 12 months analyses for the health resource utilization (HRU) endpoint and clarified the derivation of the planned treatment period number, on-study number and past 12 months per subject.	NA	Added HRU analyses including all data on study and past 12 months before study for assessment and provided clarity for TFLs.
Data presentations	5-Sep-22	Sections 3.3.2, 4.2.8.1: Addition of study adjusted incidence rate for adverse events. Updated the derivation of exposure adjusted incidence rates to be the same for all subjects, irrespective of whether they had the adverse event (AE).	NA	In line with AZ guideline on reporting safety data.
Data presentations	5-Sep-22	Section 3.3.2: Terminology “Treatment-emergent” replaced with “during on-treatment period”.	NA	For consistency with reporting periods.
Data presentations	5-Sep-22	Section 4.2.4.4: Added analysis of annualised exacerbation rates due to hospitalisations that are adjudicated.	Yes (CSP version 5.0, 17-May-22)	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Sections 4.2.4.5, 4.2.5.5: Removed text regarding bootstrapping.	NA	To avoid misinterpretation for the standardised effect plots.
Data presentations	5-Sep-22	Section 3.2.3.6: Updated means derived for individual symptom scores within the ASD would combine daytime and night-time data.	Yes (CSP version 5.0, 17-May-22)	Provided clarity for TFLs.
Data presentations	5-Sep-22	Sections 1.1.3, 3.4, 4.2.9.1: Replaced “serum trough concentration” by “serum	No	Data from follow-up visits (Week 64) will be included in the

		concentration" in the analyses and output. A footnote was added to the objective table for clarification.		analyses and is referred to as serum concentration not trough concentration.
Data presentations	5-Sep-22	Section 4.2.2: Added text noting that baseline total daily dose to be displayed would be the categories low/medium/high. Added text regarding disallowed medications.	NA	Provided additional clarification.
Data presentations	5-Sep-22	Sections 4.2.4.5, 4.2.5.5: Removed CRSwNP as subgroup for efficacy analyses.	NA	Removed subgroup that expect to have small patient number from efficacy analysis.
Data presentations	5-Sep-22	Section 4.2.5.1: Clarified that all subjects in the full analysis set (FAS) with baseline and at least one post-baseline assessment would be included in the change from baseline analyses.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.5.5: Clarified that the adjusted means at all timepoints would be summarised graphically for the FEV1 subgroup analyses and only the adjusted mean at Week 52 will be tabulated.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.6: Updated that total daily asthma symptom score would be analysed using a repeated measure model and component daytime and night-time score would only summarised descriptively.	NA	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Section 4.2.6: Added a figure summarising the cumulative number of asthma exacerbations.	NA	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Section 4.2.6: Noted that eosinophil and total serum IgE would also be	NA	Provided clarity for TFLs.

		included in the summaries of laboratory data.		
Data presentations	5-Sep-22	Section 4.2.6: Updated that morning and evening home-based PEF would be analysed using a repeated measures model instead of descriptive summary only.	NA	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Section 4.2.7: Updated that change from baseline in SNOT-22 would be summarised descriptively for all subjects and the subset of subjects who had nasal polyps in the 2 years before randomisation.	NA	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Section 4.2.8.1: Updated that AE summaries for causality and maximum intensity would be reported by preferred term (PT) only and not by system organ class (SOC) and PT.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.8.1: Updated that deaths adjudicated as cardiovascular (CV)/malignancy death would be included in the adjudication summary of major adverse cardiac events (MACE) and malignancy.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.8.2: Clarified that all summaries and figures would report laboratory data in SI units.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.8.2: Removed figure of mean changes from baseline over time for safety laboratory data summary.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Sections 4.2.8.2, 4.3.8.3: Updated that shift tables would not display missing values and shift plots would not present reference lines for normal ranges.	NA	Provided clarity for TFLs.

Data presentations	5-Sep-22	Section 4.3.8.4: Updated that Fridericia corrected QT would be summarised per pre-defined thresholds, instead of corrected QT.	NA	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.9.1: Added the category of non-treatment-emergent ADA positive in the analyses of concentration by ADA category.	NA	Required supportive analysis for CSR.
Data presentations	5-Sep-22	Section 4.2.9.2: Updated that the association of ADA status with key secondary and biomarker data may be evaluated and clarified only number of ADA positive subjects would be summarised at each visit.	Yes (CSP version 5.0, 17-May-22)	Provided clarity for TFLs.
Data presentations	5-Sep-22	Section 4.2.10: Clarified that China subpopulation would only include China patients and region (China or non-China) will not be adjusted in the China subpopulation analyses.	NA	Provided clarity for TFLs.
Other	5-Sep-22	Section 1.2: The percentage of China subjects reduced from ~80% to ~70%. The subject distribution for background ICS and screening eosinophil level changed.	Yes (CSP version 5.0, 17-May-22)	To facilitate study recruitment, while the overall sample size remains the same.
Other	5-Sep-22	Section 3.4: Updated that the study team would have access to the real ADA data during study.	Yes (CSP version 5.0, 17-May-22)	ADA is not treated as unblinding per the latest Tezepelumab data.
Other	5-Sep-22	Section 4.2.4.1: Changed study discontinuation to study withdrawal.	Yes (CSP version 5.0, 17-May-22)	Consistency of text.
Other	5-Sep-22	Section 4.2.7: Noted that the results of exploratory CompEx analyses may be presented outside of CSR.	NA	Due to the exploratory nature and computational complexity.

Other	5-Sep-22	Section 6: Addition of changes from latest CSP version 5.0.	Yes (CSP version 5.0, 17-May-22)	Mandatory section update.
Other	5-Sep-22	Appendix 8.3: Added the therapy equivalent table for ICS therapy from CSP with additional note for Budesonide as a metered dose.	Yes (CSP version 5.0, 17-May-22)	Provided clarity for TFLs.
Other	5-Sep-22	Minor updates for abbreviation and clarification.	Yes (CSP version 5.0, 17-May-22)	No changes to content. Updated for clarity and consistency.
Other	5-Sep-22	Formatting and links fixed.	NA	No changes to content. Adjusted formatting to reflect house style, and errors in links resolved.
Other	22-May-24	Sections 1, 1.2, 2.1.4, 2.2, 4.1, 4.2.4.2: two DBL timing, unblinding, activities, analyses	Yes (CSP version 7.0, 21-Sep-23)	To allow for an additional DBL once the last subject completes the planned treatment phase.
Other	22-May-24	Section 1.2: China sample size, clarified at least 70% of subjects will come from China.	Yes (CSP version 7.0, 21-Sep-23)	Consistent with CSP
Data presentations	22-May-24	Sections 2.2, 4.2.1, 4.2.8.1, 4.2.8.2: removed analyses, no delivery at all (COVID PD listing, disposition by timepoint, AE event count summary, death, SAE leading to IP discontinuation, lab shift table/plot to last post-baseline value, vital signs shift plot, vital signs change from baseline category summary)	NA	Not required for CSR.
Other	22-May-24	Section 3.1.4, 3.1.8, 3.3.2: study period, censoring, AE period update due to two DBL	Yes (CSP version	Consistent with CSP

			7.0, 21-Sep-23)	
Data presentations	22-May-24	Sections 3.1.7, 4.2.1: Removed subgroup exacerbations during medium-high dose ICS background treatment in the year before study	NA	Not required for CSR.
Data presentations	22-May-24	Sections 3.4, 4.2.9.2: Separated immunogenicity summary for China and non-China	No (CSP version 7.0, 21-Sep-23)	Different laboratories used in the 2 regions.
Data presentations	22-May-24	Sections 4.2.2, 4.2.6, 4.2.7: moved some medication analyses to Section 4.2.10 (allowed medication, OCS for exacerbation, OCS dose summary, pre-BD FEF25-75%, total daily asthma symptom score, exploratory endpoints)	NA	Clarification of exploratory analyses not required for CSR.
Statistical analysis method for the primary or secondary endpoints	22-May-24	Sections 4.2.5.1, 4.2.5.2, 4.2.5.4, 4.2.5.5, 4.2.6, 4.2.7: Changed the MMRM covariance hierarchy	NA	Provided clarity for TFLs
Data presentations	22-May-24	Section 4.2.5.5: removed standardised effect plot	NA	Not required for CSR.
Data presentations	22-May-24	Section 4.2.8.1: added related AE/SAE in the overall AE summary table	NA	Required for CSR
Data presentations	22-May-24	Section 4.2.8.1, Appendix 8.1: updated AESI category and derivation	Yes (CSP version 7.0, 21-Sep-23)	Consistent with CSP
Data presentations	22-May-24	Section 4.2.8.1: adjudication output updated	NA	Provided clarity for TFLs
Data presentations	22-May-24	Section 4.2.9.2: added condition of >10 TE ADA+ in Teze	NA	Provided clarity for TFLs

Other	22-May-24	Section 4.2.10: added a new section to place analyses outside CSR	NA	Clarification of exploratory analyses not required for CSR.
Data presentations	22-May-24	Section 4.2.11: Added some clarification for China subpopulation analyses	NA	Provided clarity for TFLs
Other	22-May-24	Section 6: added one change of analysis from protocol	NA	Provided information of change from CSP
Data presentations	22-May-24	Appendix 8.4: COVID-19 analyses updated	NA	Provided clarity for TFLs
Other	22-May-24	Appendix 8.5: corrected the primary endpoint as a ratio of exacerbation rates	NA	Correction and clarification

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5180C00021. The SAP describes the statistical analyses specified in the latest version of the clinical study protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

All analyses of the primary and secondary endpoints specified in this SAP will be performed following the primary Database Lock (DBL) and included in the clinical study report (CSR) of study D5180C00021. Additional summaries based on the final DBL will be produced as appropriate and included in the CSR addendum. Analyses, specified in Section 4.2.10, will be only performed after the final DBL for reporting outside the CSR and CSR addendum (e.g., publication). The timing of primary and final DBL is given in Section 1.2.

1.1 Study objectives

1.1.1 Primary objective

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab administered subcutaneously (SC) every 4 weeks (Q4W) on asthma exacerbations in adult subjects with severe uncontrolled asthma compared with placebo	Primary endpoint: Annualised asthma exacerbation rate (AAER) Primary outcome measure: AAER ratio versus placebo over 52 weeks

1.1.2 Key secondary objectives

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W on pulmonary function compared with placebo	Key secondary: Change from baseline in pre-dose/pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV_1) Key outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg tezepelumab SC Q4W on health status/health related quality of life compared with placebo	Key secondary: Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) total score Key outcome measure: Mean difference vs placebo at Week 52

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W on asthma control compared with placebo	Key secondary: Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) score Key outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg tezepelumab SC Q4W on asthma symptoms compared with placebo	Key secondary: Change from baseline in weekly mean daily Asthma Symptom Diary (ASD) score Key outcome measure: Mean difference vs placebo at Week 52

1.1.3 Other secondary objectives

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W on other endpoints associated with asthma exacerbations	Outcome variable: Time to first asthma exacerbation Outcome measure: Asthma exacerbation hazard ratio vs placebo over 52 weeks Outcome variable: Proportion of subjects who did not experience an asthma exacerbation over 52 weeks Outcome measure: Difference in proportions vs placebo at Week 52 Outcome variable: Annualised rate of exacerbations associated with emergency room (ER) visit or hospitalisation[a] Outcome measure: AAER ratio vs placebo over 52 weeks

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W on biomarkers	Outcome variables: Change from baseline in • fractional exhaled nitric oxide (FENO) • peripheral blood eosinophils • total serum IgE Outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg tezepelumab SC Q4W on other asthma control metrics	Outcome variables: Change from baseline in • weekly mean rescue medication use • weekly mean morning and evening peak expiratory flow (PEF) • weekly mean number of night-time awakenings Outcome measure: Mean difference vs placebo at Week 52 Further details clarifying the definitions of these endpoints are given in Section 3.2.4.3 and Section 3.2.4.4.
To assess the effect of 210 mg tezepelumab SC Q4W compared with placebo on health resource utilization due to asthma	Outcome variables: • Asthma specific resource utilization (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) Outcome measures: • Difference in number of asthma specific resource utilizations vs placebo over 52 weeks
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum trough concentrations[b] Immunogenicity: Incidence of anti-drug antibodies (ADA)

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W on general health-related quality of life	Outcome variable: European Quality of Life – 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) score Outcome measure: Mean difference vs placebo at Week 52

[a] Terminology to describe ER and urgent care visits may differ between countries. All such visits have been captured as ER visits, which will be included in the analyses and outputs.

[b] Although the protocol specifies that serum trough concentrations will be the endpoint used to evaluate the PK of Tezepelumab, data from follow-up visit (Week 64) will be included where appropriate and is referred to as serum concentrations in the analyses.

1.1.4 Safety objectives

Objective:	Endpoint/variable:
To evaluate the safety and tolerability of tezepelumab	Adverse events [Aes] (including serious adverse events [SAEs]) Vital signs Clinical chemistry/haematology/urinalysis parameters 12-lead electrocardiograms (ECGs)

1.1.5 Exploratory objectives

Objective:	Endpoint/variable:
To explore the effect of 210 mg tezepelumab SC Q4W on lung function	Change from baseline in post-BD FEV_1 and the forced expiratory flow over 25-75% of the vital capacity ($FEF_{25-75\%}$)
To evaluate the onset of effect of 210 mg tezepelumab SC Q4W	Change over time from baseline in each of FENO, pre-BD FEV_1, ACQ-6, asthma symptoms and rescue medication use
To evaluate the effect of 210 mg tezepelumab on symptom metrics of nasal polyposis	Change from baseline in SNOT-22 in subjects with co-morbid nasal polyposis at Week 52
To assess the effect of 210 mg tezepelumab compared with placebo with regards to health status of subjects with airway obstruction disease	Change from baseline in St George's Respiratory Questionnaire (SGRQ) score at Week 52.

Objective:	Endpoint/variable:
To explore the effect of 210 mg tezepelumab on Composite Endpoint for Exacerbations (CompEx) and the value of CompEx as a measure of asthma disease activity	The rate of CompEx occurrence versus placebo over 52 weeks.

1.2 Study design

This is a phase 3, regional, multicentre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the effect of 210 mg tezepelumab administered Q4W SC in adult subjects with severe uncontrolled asthma, who have a history of 2 or more exacerbations in the previous 12 months.

All subjects must have been receiving medium or high dose inhaled corticosteroids (ICS) for at least 3 months prior to screening. Further, all subjects must have been on at least one additional asthma controller medication according to standard practice of care, with or without oral corticosteroids (OCS), in the 3 months prior to screening.

A total of 396 subjects will be randomised in the study in a 1:1 ratio to either:

- Tezepelumab 210mg Q4W by SC injection, or
- Placebo Q4W by SC injection.

At least 70% of the subjects will come from China and the rest of the subjects will come from South Korea and Philippines. Randomisation will be stratified by region (China/non-China).

The randomised study population will be monitored throughout recruitment to ensure a broad subject distribution across key clinical factors, and limits may be placed on subsequent randomisation within certain subgroups if necessary. This monitoring will be performed overall and by region (China/non-China). The clinical factors which will be monitored, and the target percentages anticipated to be applied to the overall population for this monitoring, are:

- Exacerbation history in previous 12 months (approximately 40% subjects with ≥3 exacerbations; approximately 60% subjects with exactly 2 exacerbations).
- Background ICS dose level (approximately 40% subjects on medium ICS dose; approximately 60% subjects on high ICS dose).
- Eosinophil level at screening (approximately 55% subjects with <300 eosinophils/μL; approximately 45% subjects with ≥300 eosinophils/μL). The

proportions of subjects with <150 eosinophils/μL and ≥150 eosinophils/μL, and with <450 eosinophils/μL and ≥450 eosinophils/μL, will also be monitored.

The anticipated percentages for the factors of historical exacerbations and blood eosinophils will be applied to China and non-China subpopulation respectively and will be the same as the percentages applied to the overall population. The anticipated percentages for the factor of ICS dose will be different between China and non-China subpopulations (with approximately 20% medium dose ICS subjects in non-China region and approximately 50% medium dose ICS subjects in China).

The study will consist of a screening/run in period between 5-6 weeks, a planned treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks.

During the planned treatment period, investigational product (IP) will be administered Q4W starting at the randomisation visit (Week 0; Day 1), with the last administration occurring at Week 48. IP will not be administered at Week 52. Subjects who prematurely discontinue IP will be encouraged to remain in the study and undergo appropriate study visits/procedures for the full planned 52 week treatment period, despite no longer receiving treatment. At the IP Discontinuation (IPD) visit, the subject will be given the following 3 options (further details are given in the CSP Section 7.1.1):

1. The subject should be encouraged to return for all regular clinic visits and perform all scheduled assessments until he/she completes a total of 52 weeks in the study (the planned treatment period).

2. The subject will be offered follow-up on a monthly basis via telephone calls while continuing eDiary and PEF completion (no further procedures will be performed), until the subject completes 52 weeks in the study.

3. If the subject cannot or does not wish to comply with either of the options above (or any component of them, such as only telephone based visits without completion of the eDiary and PEF), then the Investigator will only contact the subject at 52 weeks post-randomisation. No study assessments will be performed prior to this contact.

Two DBLs are planned in this study. The primary DBL will be conducted after the last subject completes the 52-week double-blind treatment period; and the final DBL will be conducted after the last subject completes the last safety follow-up visit (Week 64). After the primary DBL, the study treatment allocation for subjects will become known to the sponsor staff. The blind will be maintained for the investigators, investigational site staff and subjects until the final DBL. All personnel involved with the analysis of the study will remain blinded until the primary DBL.

1.3 Number of subjects

Approximately 396 subjects will be randomly assigned to study treatment using 1:1 allocation between the two treatments. The sample size is estimated based on the primary endpoint (AAER) only.

198 subjects per treatment group are planned to be randomised, assuming a 10% dropout rate to obtain 178 completers (i.e., subject completes 52-week treatment period in the study). With 178 completers per treatment group, it is estimated that for the primary endpoint (AAER), assuming a placebo rate of CCI per year and a shape parameter of CCI (overdispersion), there will be 90% power to detect a rate reduction of CCI at a 2-sided significance level of 5%. The methodology used is as described in Keene et al.,2007, and developed further by Zhu and Lakkis, 2014. The minimum rate reduction that would yield statistical significance with the above assumptions is CCI

The study is powered based on the primary endpoint (AAER) only and not for the subsequent multiple testing procedures of the key secondary endpoints described in Section 4.1.2.

The above effect size and variability assumptions are taken from the Phase iIb tezepelumab trial as reported in Corren et al., 2017.

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, including screening failures, and will be used for the reporting of disposition.

Randomised subjects analysis set

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

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 3.1.4 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 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 (PDs).

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

2.1.4 Handling of other issues which may impact analysis sets

If it is found that any subject has been randomised on more than one occasion (contrary to the protocol) under different subject numbers, either at the same site or at different sites, then 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 these data will be documented, prior to unblinding at the primary DBL.

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 the primary DBL. Otherwise, it will be fully described in the CSR. The SAP will not be updated for this after the primary DBL.

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. In particular, this allows a subject who completes treatment according to the protocol to have their Week 52 data included as on-treatment, provided Week 52 is within the protocol visit window after the last dose of IP at Week 48.

Safety analyses

Any AE 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

All the important 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:

- Inclusion criteria deviations
- Exclusion criteria deviations
- Discontinuation criteria for investigational product (IP) met but patient not withdrawn from IP
- IP deviations
- Disallowed medications taken
- Deviations related to study procedure

- Other important deviations

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

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

The study Non-compliance Handling Plan outlines the management of PDs and includes the proposed specific categories of PDs in this trial. 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 study treatment will serve as the baseline measurement for safety variables. If there is no value prior to first dose of study treatment, then the baseline value will not be imputed, and will be set to missing.

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

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

In addition to the above general definition, the following rules for baseline will apply:

- For weekly mean scores derived from subject eDiary (including, but not limited to, ASD score) and weekly means of home-based PEF, baseline 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 date 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, haematology, clinical chemistry, urinalysis, 12-lead ECG), baseline will be defined as the last non-missing assessment prior to first dose of study treatment. If no time is recorded for an assessment, and the assessment takes place on the date of first dose of study treatment, this will be assumed to be a pre-dose assessment.

3.1.2 Absolute change from baseline

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

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

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

3.1.3 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.

3.1.4 Study periods

The following study periods are defined for analysis purposes:

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

- Planned treatment period (on-treatment and off-treatment): starting on the date of randomisation and ending on the date of the Week 52 visit or earlier study withdrawal date (for subjects not followed up until Week 52). The planned treatment period will only be applied to efficacy analyses.

- 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/follow-up period: starting one day after the end date of the 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 analyses performed following the primary DBL, the post-treatment/follow-up period is understood to include all data recorded for the primary DBL.

- On-study period (on-treatment and post-treatment/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 analyses performed following the primary DBL, the on-study period is understood to include all data recorded for the primary DBL.

3.1.5 Visit windows

All summaries and analyses, including efficacy, safety, PK and immunogenicity, which are presented by time point (e.g. "Week 52") will use a visit window to classify the data record, which is derived from the assessment date relative to the reference start date. This approach allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing (notably the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

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

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

For safety, PK and immunogenicity 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 derivations (see Section 3.1.1), and in any derivations 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 value will be used.

- If there are multiple immunogenicity samples in the same visit window with both positive and negative results, the sample with a positive result and the highest titre value will 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 3.1.4). 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 for all variables unless specified otherwise. It corresponds to the full (mostly 4-weekly) protocol scheduling for clinic visits, and will be used for all variables by default, including those variables which are not captured at every clinic visit (e.g., ECG, PK and immunogenicity variables), unless it is indicated below that the visit windows in Table 2 or Table 3 should be used. Additional rules for the visit window of PK variables are specified in Section 4.2.9.1.

Table 1 Visit windows – all variables where not specified otherwise

Time Point	Target Day	Visit Window
Baseline (Week 0)	1	See Section 3.1.1 for baseline definitions
Week 2	15	2-21
Week 4	29	22-42
Week 8	57	43-70
Week 12	85	71-98
Week 16	113	99-126
Week 20	141	127-154
Week 24	169	155-182
Week 28	197	183-210
Week 32	225	211-238
Week 36	253	239-266
Week 40	281	267-294
Week 44	309	295-322
Week 48	337	323-350
Week 52	365	351-385
Follow-up Week 58	407	386-427
Follow-up Week 64	449	428-469

Table 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.

Table 2 Visit windows – EQ-5D-5L only

Time Point	Target Day	Visit Window
Baseline (Week 0)	1	See Section 3.1.1 for baseline definitions
Week 2	15	2-21
Week 4	29	22-35
Week 6	43	36-49

Time Point	Target Day	Visit Window
Week 8	57	50-63
Week 10	71	64-77
Week 12	85	78-91
Week 14	99	92-105
Week 16	113	106-119
Week 18	127	120-133
Week 20	141	134-147
Week 22	155	148-161
Week 24	169	162-175
Week 26	183	176-189
Week 28	197	190-203
Week 30	211	204-217
Week 32	225	218-231
Week 34	239	232-245
Week 36	253	246-259
Week 38	267	260-273
Week 40	281	274-287
Week 42	295	288-301
Week 44	309	302-315
Week 46	323	316-329
Week 48	337	330-343
Week 50	351	344-357
Week 52	365	358-371

Table 3 summarises 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, SGRQ score, SNOT-22 score and post-BD spirometry. For post-baseline assessments scheduled in the protocol, SNOT-22 score will be assessed at Week 28 and Week 52, and weight, SGRQ score and post-BD spirometry will be assessed at Week 24 and Week 52.

Table 3 Visit windows – sparse protocol schedule

Time Point	Target Day	Visit Window
Baseline (Week 0)	1	See Section 3.1.1 for baseline definitions
Week 24 (not SNOT-22)	169	141-196
Week 28 (SNOT-22 only)	197	169-224
Week 52	365	337-392

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.

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.

3.1.6 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 NA (i.e., medication still 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/follow-up 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.

3.1.7 Definition of subgroups

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

- *Baseline eosinophils group: <300/ µ L, ⩾300/ µ L
- *Baseline eosinophils group: <150/ µ L, 150-<300/ µ L, 300-<450/ µ L, ≥450/ µ L
- *Baseline eosinophils group: <150/ µ L, ⩾150/ µ L
- *Baseline FENO group: <25ppb, ≥25ppb
- *Baseline FENO group: <25ppb, 25-<50ppb, ≥50ppb
- *ICS dose at study entry: medium, high (as defined in CSP Appendix F)
- *OCS at baseline: present, absent
    - Note: OCS at baseline will be defined as OCS administered on the date of first dose of IP (as recorded in MINT eCRF page)

- *Age category: ⩾18 to <65, ⩾65
- *Gender: Male, Female
- *Exacerbations in the year before study: ≤2 exacerbations, >2 exacerbations
    - Note: no subjects are permitted to be randomised with a history of fewer than 2 exacerbations according to the eligibility criteria. However, the definition "≤2" is used for analysis purposes, to prevent exclusion of a subject from the primary analysis in the unlikely event of an important PD in this regard.
- *Baseline BMI: <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2*Region: China, non-China (South Korea, Philippines)
- Chronic rhinosinusitis with nasal polyps (CRSwNP) status at study entry: Yes, No
    - Note: CRSwNP status at study entry will be defined by the presence of the following on the Respiratory Disease History eCRF page for a particular subject: Nasal polyps plus at least one of (Diagnosis of rhinitis; Diagnosis of chronic sinusitis).
- Nasal polyps status at study entry: Yes, No
    - Note: Nasal polyps status at study entry will be defined by the presence of nasal polyps on the Respiratory Disease History eCRF page for a particular subject.
- Nasal polyps in the 2 years before randomisation: Yes, No
    - Note: Nasal polyps in the 2 years before randomisation will be defined by the presence of nasal polyps on the Respiratory Disease History eCRF page for a particular subject, with no associated stop date on the Medical History eCRF, or an associated stop date less than or equal to 24 months before randomisation.
- Chronic sinusitis status at study entry: Yes, No
    - Note: Chronic sinusitis status at study entry will be defined by the presence of chronic sinusitis on the Respiratory Disease History eCRF page for a particular subject.
- Rhinitis status at study entry: Yes, No
    - Note: Rhinitis status at study entry will be defined by the presence of rhinitis on the Respiratory Disease History eCRF page for a particular subject.

3.1.8 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 – 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 – date of randomisation] + 1.

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

Subjects who did not prematurely withdraw from study will be censored at the following date:

- "Completion or discontinuation date" from the "Disposition" eCRF page, where subject status of "Completed" has been entered.
- For analyses performed following the 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 Annualised asthma exacerbation rate over 52 weeks

An asthma exacerbation is defined in the CSP as a worsening of asthma that leads to any of the following:

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

- An emergency room (ER) or urgent care (UC) 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 systemic corticosteroids, ER or UC visits requiring systemic corticosteroids, or hospital admissions due to asthma, whichever occurs earlier. The end date is defined in the CSP as the last day of systemic corticosteroids or 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 end 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.

Note: The protocol defined exacerbations will be recorded on the exacerbation "EXACATE" eCRF page. Terminology to describe ER and UC visits may differ between countries. All such visits have been captured as ER visits on the eCRF page that will be included in the analyses.

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 17/EOT Week 52 (expected to be the majority of subjects), then:

> *Time at risk (days) = [earliest (date of Visit 17; date of last assessment of exacerbation status from the "EXACD" eCRF page) – date of randomisation] + 1.*

Otherwise, if no Visit 17/EOT Week 52 is available for a subject:

> *Time at risk (days) = [earliest (randomisation date + 364 days + 5 days; date of last assessment of exacerbation status) – date of randomisation] + 1,*
>
> *where:*

Date of last assessment of exacerbation status = Latest of:

1. *the date of last assessment of exacerbation status from the "EXACD" 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 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 "EXACD" eCRF page might be later than the last available visit during the planned treatment period, e.g., in the case that the subject remained in the study with incomplete follow-up options after early discontinuation of IP.

For the primary 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 this time point will not be included in analyses.

3.2.2 Key secondary endpoints

3.2.2.1 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 52 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.

3.2.2.2 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
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 key secondary endpoint for the AQLQ(S) +12 will be the change in total score from baseline at Week 52. 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.

3.2.2.3 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 key secondary endpoint for the ACQ-6 will be the change in mean score from baseline at Week 52, 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.

3.2.2.4 Change from baseline in weekly mean daily Asthma Symptom Diary (ASD) score

Asthma symptoms during night-time and daytime will be recorded by the subject each morning and evening in the 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 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 following morning. The daytime ASD score is defined as the mean of 5 items recorded in the evening and the night-time ASD score is the mean of 5 items recorded the following morning. If 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 score 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.

3.2.3 Additional endpoints supporting primary and key secondary endpoints

3.2.3.1 Other annualised exacerbation rates

To assess the effect of tezepelumab on other endpoints associated with asthma exacerbations, an annualised rate of exacerbations associated with ER visit or hospitalisation will be chosen as a secondary endpoint (a subset of the primary endpoint defined in Section 3.2.1.1, specifically the 2nd and 3rd bullets only).

An annualised rate of exacerbations associated with hospitalisation only will also be derived (a subset of the primary endpoint defined in Section 3.2.1.1, specifically the 3rd bullet only).

Note that the primary endpoint does not consider adjudicated outcomes at all in the definition given in Section 3.2.1.1. 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 3.2.1.1. 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 Other clinic visit pre-BD spirometry

The details of derivation of other clinic visit pre-BD spirometry endpoints are like those in Section 3.2.2.1:

1. Pre-BD $FEF_{25-75\%}$

2. Pre-BD FEV_1/FVC ratio.

3.2.3.3 AQLQ(S)+12 and ACQ-6 responders

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.

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.

3.2.3.4 ACQ-5 and ACQ-7

The ACQ-5 score is the same as ACQ-6 score as defined in Section 3.2.2.3, with the removal of item #6 "daily rescue medication". An unweighted mean is calculated from the remaining 5 items.

The ACQ-7 score is the same as ACQ-6 score as defined in Section 3.2.2.3, with the addition of an item scored 0-6 for pre-BD FEV_1 % predicted (see below). FEV_1 % predicted will be provided directly (to 2 decimal places) in the spirometry data transfer:

- 0: >95.00%
- 1: 90.00-95.00%
- 2: 80.00-89.99%
- 3: 70.00-79.99%
- 4: 60.00-69.99%
- 5: 50.00-59.99%
- 6: <50.00%

An unweighted mean is calculated from all 7 items.

3.2.3.5 Asthma symptomatic days

The number of asthma symptomatic days will be calculated for each week for each subject as the number of days for which the ASD score (i.e. mean of 10 items) ≥ 1. The definition of day and week are as given in Section 3.2.2.4.

Change from baseline in the percentage of symptomatic days (out of the number of available days within the week) will be calculated at each post-baseline week. If more than 3 days are missing within any week, this percentage will remain missing for that week.

3.2.3.6 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 only)
- Limit activities (daytime item only).

Weekly means will be calculated similarly to those specified in Section 3.2.2.4.

3.2.3.7 ASD responders

The following will be reported at each time point:

ASD responder (Yes=1/No=0):

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

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

3.2.4 Other secondary endpoints

3.2.4.1 Other exacerbation endpoints

Time from randomisation to the first asthma exacerbation will also be used as a supportive endpoint to the primary objective, and is calculated as follows:

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

This analysis will only be done on the planned treatment period (see Section 3.1.4). Subjects without an exacerbation will be censored at the end of the time at risk for exacerbation, as defined in Section 3.2.1.

Time from randomisation to first asthma exacerbation due to hospitalisations or ER visits will also be calculated, similarly to above.

The proportion of subjects who had no asthma exacerbations during the planned treatment period will also be calculated. A subject will be considered to have completed the planned treatment period (to Week 52), if the subject's follow-up time is greater than 359 days (Day 364 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 will be defined as exacerbation free [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 at least one asthma exacerbation during the planned treatment period will be defined as not having a successful outcome for this endpoint [d].

	No exacerbation	≥ 1 exacerbation
Completed planned treatment period	[a] Exacerbation free /successful outcome	[d] No successful outcome
Did not complete planned treatment period	[b] No successful outcome	[c] No successful outcome

The proportion will be calculated for each treatment group as:
Number of subjects who were exacerbation free [a] / number of subjects in treatment group.

The proportion of subjects free from exacerbations that required ER visits or hospitalisations during the planned treatment period will also be calculated similarly. A subject who only had exacerbations which did not lead to hospitalisations or ER visits will also be considered a successful outcome for this endpoint.

3.2.4.2 Biomarkers

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

- FENO (ppb)
- Peripheral blood eosinophils (10**9/L and Cells/µL)
- Total serum IgE (mg/L and IU/mL)

The definition of baseline is given in Section 3.1.1.

For FENO, it is expected that one technically acceptable measurement will be performed at each relevant clinic 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 3.1.5).

3.2.4.3 Additional endpoints from subject eDiary

To assess the effect of tezepelumab on other asthma control metrics, additional questionnaires to the ASD will be administered to collect rescue medication, night-time awakening and total daily asthma symptom score.

The total daily asthma symptom score is derived from the Global Asthma Symptom item assessment each morning (night-time asthma symptom score) and evening (daytime asthma symptom score), used for the alerts system. This is not the same as the daily score derived from the ASD.

The following endpoints will be derived:

- weekly mean rescue medication use
- weekly mean number of night-time awakenings requiring rescue medication
- weekly mean total daily asthma symptom score
- weekly mean daytime asthma symptom score
- weekly mean night-time asthma symptom score

In the endpoints described in this section, where relevant, one day is defined as the evening measurement followed by the measurement of the following morning.

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 night-time 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 daytime inhaler puffs + 2 x [number of daytime nebulizer times].

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

Night-time awakenings requiring rescue medication

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.

Total daily asthma symptom score

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. Daytime asthma symptom score (recorded in the evening), night-time asthma symptom score (recorded in the following morning) and total daily asthma symptom score will be calculated and presented separately.

The total daily asthma symptom score will be calculated by taking the sum of the daytime asthma symptom score and the night-time asthma symptom score. 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 daily asthma symptom 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 3.2.2.4.

3.2.4.4 Home-based peak expiratory flow (PEF)

Change from baseline in weekly mean morning and evening 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 3.2.2.4.

3.2.4.5 Health resource utilization (HRU)

HRU due to asthma will be recorded in the “Asthma-Related Events, since Previous 12 months (HEVENT)” and “Asthma-Related Events, since Previous Visit (HEVENT1)” module of the eCRF.

The planned treatment period number of days/times, the on-study number of days/times, and the past 12 months number of days/times will be calculated for each subject for the following variables, where applicable:

- Ambulance transport
- Hospitalisation
    - 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 planned treatment period number per subject will be determined as:

> *Planned treatment period number = Sum of 'number of times/days' as entered on the HEVENT1 eCRF page post-randomization up to Week 52.*

The on-study number per subject will be determined as:

On-study number = Sum of 'number of times/days' as entered on the HEVENT1 eCRF page post-randomization up to Week 64.

The past 12 months number per subject will be determined as:

Past 12 months number = 'number of times/days' as entered on the HEVENT eCRF page at visit 1 or rescreening visit 1.

3.2.4.6 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.

3.2.5 Exploratory endpoints

3.2.5.1 Clinic visit post-BD spirometry

The details of derivation of clinic visit post-BD spirometry endpoints are like those in Section 3.2.2.1 :

1. Post-BD FEV_1
2. Post-BD $FEF_{25-75\%}$
3. Post-BD FEV_1/FVC ratio.

3.2.5.2 SNOT-22 score

The SNOT-22 is a 22-item health-related outcomes assessment for sinonasal conditions. Each item is scored as 0 (no problem) to 5 (problem as bad as it can be). The total SNOT-22 score is the sum of the 22 items and it ranges from 0 to 110 (higher scores indicate poorer outcomes).

If one or more of the individual items is missing, the total SNOT-22 score will be missing.

The change from baseline in total SNOT-22 score will be calculated for each post-baseline time point.

3.2.5.3 SGRQ score

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

Change from baseline will be calculated for the total SGRQ score and the 3 domain scores. In addition:

- an SGRQ responder will be defined as a subject with a change from baseline in total score ≤ -4 (i.e. a reduction of 4 or more).
- a deterioration in SGRQ will be defined as a change from baseline in total score ≥ 4 (i.e. an increase of 4 or more).

3.2.5.4 Annualised CompEx rate

The CompEx endpoint (see Fuhlbrigge et al, 2017) may allow the design of shorter trials which require fewer subjects than studies of severe exacerbations, whilst possibly preserving the ability to show a treatment effect compared with severe exacerbations. This will be investigated in an exploratory way in this trial.

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

1. An asthma exacerbation (as defined for the primary endpoint in Section 3.2.1.1),

2. An objective deterioration, which is defined as either the threshold criterion or the slope criterion (or both), as defined below, being met for ≥2 consecutive days.

   For this purpose, "2 consecutive days" means strictly the same 2 consecutive days when assessing multiple requirements within those days. For eDiary data captured twice during the day, one day will be defined by the morning/evening pairing for consistency with published precedent for the CompEx endpoint. (Note: other eDiary endpoints in this trial will use an evening/morning pairing to define one day.)

   Threshold criterion:

   a. ≥15% decrease from baseline in either morning or evening home-based PEF,

and at least one of the following:

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

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

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

For (c), the asthma symptom score (scored 0-3) as described in Section 3.2.4.3 will be used, recorded in the morning and evening, respectively. The maximal symptom score is therefore 3.

Assessment of the threshold criterion in any rolling 2-day consecutive period will be based on the available data during that period. The threshold criterion can be met with non-missing values for fewer than the 6 variables specified above, provided those non-missing values meet the criterion.

Slope criterion:

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

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

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

In all of the above cases, the regression slope is the point estimate of the slope obtained from a linear regression of the absolute values of each of the 6 variables separately against day number, with no other variables included in the regression model.

For morning and evening PEF, the regression slope thus obtained will first also be divided by the baseline PEF value before applying the above criterion.

The following table shows how the timing for the 5 day requirement for the regression slopes fits with the 2 consecutive day requirement, where "Day 0" here refers to the first of the 2 consecutive days (shaded) to be used each time the rolling 2 consecutive day assessment is made:

Table 5 Timing for assessment of CompEx slope criterion

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

A regression slope will be calculated provided there are at least 2 non-missing values in the required 5 days. If one or more of the 6 variables above does not have at least 2 non-missing values in the required 5 days, then the slope requirement therefore cannot be met.

The start date of a CompEx event is defined as the earliest of the exacerbation or objective deterioration start dates which meets the definition. Exacerbation start date is as stated in Section 3.2.1.1. Objective deterioration start date is defined as the earliest Day 0 (in notation from above table) from any series of rolling 2 consecutive days which first qualifies using either the threshold or slope criterion.

The end date of a CompEx event is defined as the latest of the exacerbation or objective deterioration end dates which meets the definition. Exacerbation end date is as stated in Section 3.2.1.1. Objective deterioration end date is defined as the latest Day 1 (in notation from above table) from any series of rolling 2 consecutive days which last qualifies using either the threshold or slope criterion.

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

Time at risk will be defined similarly as for the primary endpoint in Section 3.2.1.1, with assessment of last exacerbation status widened to also include additional consideration of last assessment of the various eDiary and home PEF items used in the CompEx derivation.

3.3 Derivation of safety variables

3.3.1 Exposure to IP and treatment compliance

Extent of exposure to IP is defined as the number of days between the date of first dose of IP and the date of last dose of IP inclusive plus the number of days allowance for the dosing interval specified in Section 2.1.5, that is:

Extent of exposure (days) = minimum (date of last dose of IP + 33 days; date of death; date of study withdrawal) – date of first dose of IP + 1

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

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

Treatment compliance will be calculated as follows:

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

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

3.3.2 Adverse events (AE) – general

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

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

- AEs occurring during screening/run-in period: date of Visit 1 ≤ AE onset date < date of first dose of Ip.
- AEs occurring during on-treatment period: date of first dose of IP ≤ AE onset date ≤ minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal).
- AEs occurring during post-treatment/follow-up period (for subjects still being followed up then): date of last dose of IP + 33 days < AE onset date ≤ study completion or withdrawal date. Note: for the analyses performed following the primary DBl, AEs occurring during post-treatment/follow-up period (for subjects ongoing at primary DBL): date of last dose of IP + 33 days < AE onset date.

- AEs occurring during on-study period: date of first dose of IP ≤ AE onset date ≤ study completion or withdrawal date. Note: for the analyses performed following the primary DBl, AEs occurring during on-study period (for subjects ongoing at primary DBL): date of first dose of IP < AE onset date.

If the AE has a completely missing (and unresolvable) onset date, then the AE will be assumed to have occurred during the on-treatment period, unless the end date indicates unambiguously that the AE resolved before treatment started.

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

Exposure adjusted incidence rates for a treatment group will be defined as the number of subjects reporting AEs divided by the total subject-years exposure (defined in Section 3.3.1) for that treatment group, irrespective of whether the subject has 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.

Study adjusted incidence rates for a treatment group will be defined as the number of subjects reporting AEs divided by the total duration of the on-study period across all subjects for that treatment group, where duration of the on-study period is defined as in Section 3.1.4.

3.3.3 Adverse events of special interest (AESI)

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

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 pregnancy samples will be analysed by the central laboratory only when a positive pregnancy urinalysis result for any parameter is observed locally.

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

In all 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 3.1.5).

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 result 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 BMI) will be calculated at relevant visits as specified in Section 3.1.1 and Section 3.1.2.

BMI is calculated as follows, where height at baseline is used in calculation throughout:

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 6 Vital signs reference ranges

Parameter	Standard Unit	Lower Limit	Upper Limit	Change from Baseline Criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (sitting)	mmHg	90	160	±30

Parameter	Standard Unit	Lower Limit	Upper Limit	Change from Baseline Criteria
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 electrocardiogram (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 ECG variables (data provided external to the eCRF) will be calculated at relevant visits as specified in Section 3.1.1 and Section 3.1.2.

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.

3.4 Derivation of pharmacokinetic (PK) and immunogenicity variables

Serum samples for determination of tezepelumab concentrations and the presence of ADA and neutralising antibodies (nAb) will be collected at baseline prior to first IP administration, at selected 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.

ADA samples from participants in China and samples from participants outside of China will be tested separately in different central laboratories.

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 ADA 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 real PK 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 summary will be available (for the tezepelumab group only); no PK parameters will be derived for any analysis within the scope of this SAP.

4. ANALYSIS METHODS

4.1 General principles

Two DBLs are planned in this study. The primary DBL will be conducted after the last subject completes the 52-week double-blind treatment period. The final DBL will be conducted after the last subject completes the last safety follow-up visit (Week 64).

After the primary DBL, the study treatment allocation for subjects will become known to the sponsor staff. The blind will be maintained for the investigators, investigational site staff and subjects until the final DBL. All personnel involved with the analysis of the study will remain blinded until the primary DBL.

Unless otherwise specified, all analyses of the primary and secondary endpoints will be performed following the primary DBL date for the CSR, including all data recorded up until the data cut-off date for the primary DBL. The analyses that are relevant to the 12-week post-treatment follow-up data (e.g., safety, PK, immunogenicity) will be re-run based on the full data following the final DBL date as appropriate, and the updated results will be included the CSR addendum. Where applicable, some analyses (e.g., exploratory endpoints) will be only performed after the final DBL for reporting outside the CSR and CSR addendum (e.g., publication) and such analyses are described in Section 4.2.10.

4.1.1 Statistical hypotheses for confirmatory endpoints

The following two-sided hypotheses will be evaluated in this trial. The nominal significance

levels and methodology for accounting for multiplicity in testing these hypotheses is described in Section 4.1.2.

Primary endpoint

H01: AAER ratio over 52 weeks (tezepelumab/placebo) = 1

versus

H11: AAER ratio over 52 weeks (tezepelumab/placebo) ≠ 1

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

Key secondary endpoints

H02: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) = 0

versus

H12: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means greater than 0.

H03a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) = 0

versus

H13a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means greater than 0.

H03b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) = 0

versus

H13b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means less than 0.

H04: Difference in mean change from baseline in weekly mean daily ASD score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14: Difference in mean change from baseline in weekly mean daily ASD score at 52 weeks (tezepelumab minus placebo) ≠ 0

The direction of superiority of tezepelumab is indicated by a difference in means less than 0.

4.1.2 Testing strategy for confirmatory endpoints

The overall Type 1 error rate will be strongly controlled at the 0.05 level across the primary and key secondary endpoints. The following hierarchical testing strategy will be applied, ordered by clinical relevance:

Level 1

The null hypothesis H01 will be tested at a 2-sided 5% significance level regarding the primary endpoint (AAER).

Level 2

If H01 is rejected at the 2-sided 5% significance level, then the null hypothesis H02 will be tested at a 2-sided 5% significance level regarding change from baseline in pre-BD FEV_1.

Level 3

If H02 is rejected at the 2-sided 5% significance level, then the null hypotheses H03a and H03b will be simultaneously tested at an overall 2-sided 5% significance level regarding:

- change from baseline in AQLQ(S)+12 total score
- change from baseline in ACQ-6 score

using a truncated Hochberg approach. In general, under this approach, the higher of the two ordered p-values within Level 3 will be evaluated at a $\gamma\alpha + (1-\gamma)\alpha/2$ significance level (2-sided), and the lower of the 2 ordered p-values within Level 3 will be evaluated at a $\gamma\alpha/2 + (1-\gamma)\alpha/2$ significance level (2-sided), where $\alpha = 0.05$, and where γ is the truncation parameter ($0 \leqslant \gamma \leqslant 1$).

It is noted an intermediate choice $0 < \gamma < 1$ of the truncation parameter represents a choice between these extremes of regular Hochberg (corresponding to $\gamma = 1$) and Bonferroni approaches ($\gamma = 0$), balancing considerations of how stringent hypothesis testing should be in

Level 3 in order to claim significance, versus the ability to subsequently claim significance from formal hypothesis testing in Level 4. In this trial γ will be set to 0.5.

Using this choice of truncation parameter, the higher of the two Level 3 p-values will be evaluated at a 3.75% significance level (2-sided). If it is significant at the 3.75% level, then both hypotheses H03a and H03b will be rejected, and testing will proceed to Level 4. If it is not significant at the 3.75% level, then the lower of the 2 Level 3 p-values will be evaluated at a 2.5% significance level (2-sided). If it is significant, then the relevant null hypothesis (either H03a or H03b) will be rejected, and testing will proceed to Level 4. If it is (also) not significant, then formal testing will stop at Level 3. The significance levels for subsequent evaluation in Level 4 for each of these scenarios are given below.

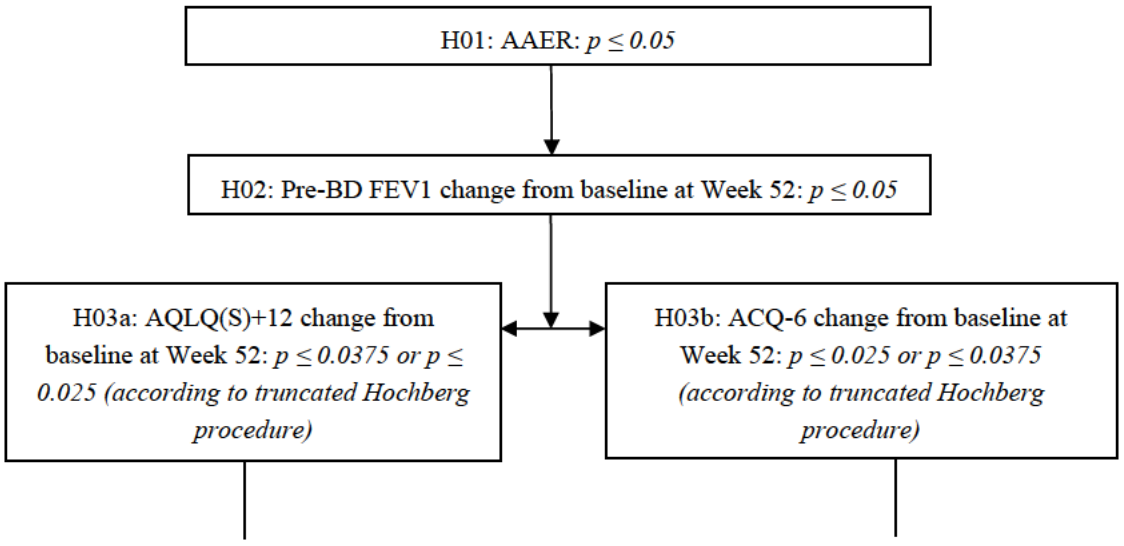
Level 4

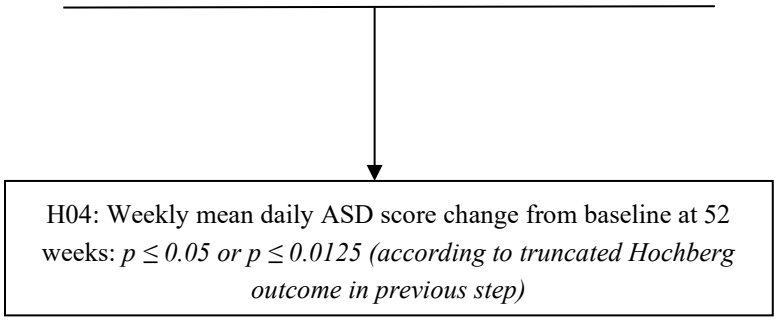
The null hypothesis H04 will be tested at the significance level retained from Level 3, which depends on the outcomes in Level 3 as follows:

- Case 1: If both comparisons in Level 3 exhibit statistical significance, then H04 will be tested at a 2-sided 5% significance level with regard to change from baseline in weekly mean daily ASD score.
- Case 2: If only one of the comparisons in Level 3 exhibits statistical significance, then H04 will be tested at the 2-sided significance level $\alpha - [\gamma \alpha + (1-\gamma)\alpha/2]$ retained from Level 3, where $\alpha = 0.05$.

Using the proposed choice of $\gamma = 0.5$, if both H03a and H03b were rejected in Level 3, then H04 in Level 4 will be tested at a 2-sided 5% significance level (Case 1). If only one of H03a and H03b was rejected in Level 3, then H04 in Level 4 will be tested at a 2-sided 1.25% significance level (Case 2).

The multiple testing procedure is summarised graphically in the following figure:





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 (and reason). Subject recruitment by country and centre will also be summarised.

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 3.1.8.

Demographic data, such as age, gender and race, will be summarised by treatment group for the FAS. Stratification factor recorded at randomisation by the IXRS will be summarised by treatment for the FAS. All subgroups as defined in Section 3.1.7 will be summarised (frequency and percentage) 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, the 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 PDs 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.

4.2.2 Prior and concomitant medication

The number and percentage of subjects receiving each medication (by ATC classification system code and generic term) will be presented by treatment for the FAS. Separate tables will be presented for the disallowed prior medications, the disallowed concomitant medications during on-treatment period, the disallowed concomitant medications during post-treatment/follow-up period, the disallowed prior biologics, and the allowed concomitant medications during on-treatment period. The medication categories are defined in Section 3.1.6..

Disallowed medications will include medications defined as prohibited according to Section 6.5 of the CSP. Disallowed medications will also include restricted medications, which 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 Section 6.5 of the CSP. They will be defined following a physician review (prior to the primary database lock) of the unique combinations of ATC code classifications and generic terms captured.

Tables for maintenance medications (started prior to and ongoing after the date of first dose of IP) will be produced displaying the baseline total daily dose categories (low/medium/high) of ICS medications. The number of subjects using other maintenance asthma medications at baseline will also be summarised.

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.

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, using 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.

4.2.4 Primary endpoint

4.2.4.1 Primary analysis

The primary analysis of the primary efficacy endpoint (AAER over 52 weeks) will quantify the effect of the initially randomised treatment, regardless of the treatments that subjects actually received, or whether the subjects received other controller therapy/rescue medications post IP discontinuation. This analysis will use FAS and include all available data after treatment discontinuation until the end of the planned treatment period. The details regarding the primary estimand for the primary endpoint are specified in Appendix 8.5.

Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 52-week period even after premature discontinuation of IP. Consequently, subjects lost to follow-up 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 perform the statistical test of the null hypothesis specified in Section 4.1.1 and to estimate the treatment effect and its 95% confidence intervals (CIs).

The response variable in the model will be the number of asthma exacerbations experienced by a subject over the 52-week planned treatment period (or shorter duration if not followed up for the full 52 weeks). Treatment, region (China or non-China) and history of exacerbations (<=2 or >2 in previous 12 months) will be included as factors in this model. If applicable, any subject who is incorrectly randomised with a history of fewer than 2 exacerbations will be included in the primary analysis. The logarithm of the time at risk (in years) for exacerbation 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 all further primary endpoint derivation details, see Section 3.2.1.

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 group divided by the total time at risk for that treatment group).

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

4.2.4.2 Sensitivity analyses

Controlled imputation

To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions about missing data, controlled multiple imputation analyses will be performed which allow 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 MAR and dropout reason-based multiple imputation (DRMI) (missing not at random (MNAR)) assumptions respectively:

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

b) DRMI (MNAR): Missing counts will be imputed differently depending on the reason for dropout in the tezepelumab group.

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

   Table 7 summarises how subjects withdrawing from study in tezepelumab group 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.

Although death is not the source of missing data, imputations (MAR and DRMI) will still be performed to assess the impact of no data after death in the primary analysis. Given the expectation that very few deaths (if any) would be observed in this study, the impact is expected to be minimal.

Table 7 Treatment used in the imputation of tezepelumab subjects under DRMI

Reason for withdrawing from study	Reason for discontinuing IP	DRMI
Death		Placebo
Adverse event		Placebo
Site terminated by sponsor		Tezepelumab
Lost to follow-up, Withdrawal by subject, Other	Adverse event	Placebo
	Development of study-specific discontinuation criteria	Placebo
	Severe non-compliance to protocol	Placebo

Reason for withdrawing from study	Reason for discontinuing IP	DRMI
	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 discontinued IP for reasons of "Subject lost to follow-up", "Subject decision" or "Other" will be performed prior to unblinding at the primary database lock. A listing of these subjects and the assumptions made under DRMI will be documented. If any recorded comments (on either of the "Discontinuation of Investigational Product" or "Disposition" eCRF pages) indicate clearly that the dropout reason was not related to treatment, then the "Placebo" default for DRMI in the above table may be changed to "Tezepelumab" for that subject.

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, region (China or non-China) and history of exacerbations (<=2 or >2 in previous 12 months) 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 the parameter k and regression 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 assumptions, 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 withdrew 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 withdrew from the study early.

iv. A negative binomial regression model will be fitted using Y_3 as the response variable, with treatment, region (China or non-China) and history of exacerbations (<=2 or >2 in previous 12 months) 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 subtracting the time during an observed exacerbation and the 7 days following an observed exacerbation.

v. Using the model from (iv) calculate treatment difference estimates 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 difference estimates in (v) to give an overall treatment difference estimate 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 overall estimate 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 group, 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.

Additional sensitivity analyses to assess the impact of the COVID-19 pandemic on the primary analysis results are specified in Appendix 8.4.

4.2.4.3 Supplementary analyses

The primary 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.

4.2.4.4 Supporting analyses

Annualised rates for those exacerbations due to ER visits or hospitalisations (a subset of the primary endpoint defined in Section 3.2.1.1, specifically the 2nd and 3rd bullets only) will be summarised descriptively and analysed using a similar model as for the primary analysis.

Annualised rates for those exacerbations due to hospitalisations only (a subset of the primary endpoint defined in Section 3.2.1.1, specifically the 3rd bullet 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. The analysis which considers adjudicated outcomes will also be performed for the exacerbations due to ER visits or hospitalisations and exacerbations due to hospitalisations only.

Analysis of the time to first exacerbation is described in Section 4.2.6, since this is defined as a secondary endpoint.

4.2.4.5 Assessing efficacy across phenotypes and other baseline characteristics

Efficacy for the primary endpoint will be evaluated separately for biomarkers of interest (which comprises an evaluation of both categorical subgroups and the continuous biomarker variable), and other exploratory variables (which comprises an evaluation of categorical subgroups only).

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

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

Biomarkers of interest

Descriptive summaries of the AAER by treatment group will be produced for each of the following categorical variables:

- Baseline eosinophils group: <300/ µ L, ⩾300/ µ L
- Baseline eosinophils group: <150/ µ L, 150-<300/ µ L, 300-<450/ µ L, ≥450/ µ L

- Baseline eosinophils group: <150/ µ L, ⩾150/ µ L
- Baseline FENO group: <25ppb, ≥25ppb
- Baseline FENO group: <25ppb, 25-<50ppb, ≥50ppb

A similar negative binomial model will be fitted as for the primary analysis for each of the above variables in turn, with additional factors for the subgroup variable and the treatment by subgroup interaction. This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories, which will be tabulated and also summarised graphically using a forest plot. The overall treatment effect will be displayed on the forest plot as well.

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, which arise from both low power and an inflated chance of false positive findings.

The probability of a chance finding will be assessed using a standardised effect plot. This plot will present the estimated effects for each subgroup category (estimated from the above models and ordered from largest to smallest), for all subgroup variables together as listed above, along with reference lines for what would be expected for the most extreme observations by chance (when there was no treatment by subgroup interaction), as taken from a permutation distribution. Observed values falling outside of these reference lines will be investigated further in terms of the plausibility and causes of such an effect. Further graphical analysis may be performed to aid interpretation if necessary.

Any unexpected observed pattern may also be further explored using resampling techniques, where null hypothesis data will be generated (in many iterations) to assess the probability of seeing a pattern as strong (or stronger) by chance only; the null hypothesis will correspond to keeping the main effects intact whilst breaking any potential predictive property of the biomarkers.

A locally estimated scatterplot smoothing (LOESS) plot will be produced for each of the continuous biomarker variables (baseline eosinophils (cells/µL), baseline FENO (ppb) and baseline total serum IgE (IU/mL)).

Other exploratory variables

Descriptive summaries of the AAER by treatment group will be produced for each of the following categorical variables:

- ICS dose at study entry: medium, high
- Age category: ⩾18 to <65, ≥65
- Gender: Male, Female

- Exacerbations in the year before study: ⩽2 exacerbations, >2 exacerbations
- OCS at baseline: present, absent
- Baseline BMI: <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2
- Region: China, non-China

A similar negative binomial model will be fitted as for the primary analysis for each of the above variables in turn, with additional factors for the subgroup variable (where not already included) and the treatment by subgroup interaction. This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories, which will be tabulated and also summarised graphically using a forest plot. The overall treatment effect will be displayed on the forest plot as well.

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.

The standardised effect plot will be produced for:

- Subgroups defined using pre-specified categories (biomarkers of interest and other exploratory variables on the same plot)

4.2.5 Key secondary endpoints

4.2.5.1 Main analysis

The main analysis of the key secondary endpoints (changes from baseline to Week 52 for each of pre-BD FEV_1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean daily ASD score) will quantify the effect of the initially randomised treatment at Week 52, regardless of the treatments that subjects actually received or whether the subjects received other controller therapy/rescue medications, including subjects who discontinued study treatment prior to Week 52. All subjects in the FAS with baseline and at least one post-baseline assessment will be included in the analysis. This analysis will include all available data after treatment discontinuation until the end of the planned treatment period. The details regarding the estimand for the key secondary endpoints are specified in Appendix 8.5.

Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 52-week period even after premature discontinuation of IP. Consequently, subjects lost to follow-up, subjects who withdrew their consent, and subjects who chose Option 2 or 3 for their follow-up should be the only source of missing information for the key secondary analyses.

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 for the key secondary endpoints in the tezepelumab group will be compared to that seen in the placebo group using a linear model for repeated measures. In this model, inference will be based on the restricted maximum likelihood (REML) estimation. This model will be used to perform the statistical tests of the null hypotheses specified in Section 4.1.1, and to estimate the treatment effect at Week 52 and its 95% CI, for each endpoint.

The response variable in the model will be the change from baseline at each scheduled post-randomisation visit up to and including Week 52, and irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region (China or non-China) 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. Baseline by visit interaction will not be included as a covariate in this model. Note: for the ASD endpoint, each of the 52 weeks used for weekly mean calculation will replace visit in the above model specification.

This linear model for repeated measures will be fitted using the SAS PROC MIXED, in which no RANDOM statement will be specified as no random effect will be included and subject will be included in this model using the REPEATED statement to specify the covariance matrix for the random error.

For all the key secondary endpoints, the unstructured covariance will be assumed to model the relationship between pairs of response variables taken at different visits on the same subject. If the unstructured covariance structure fails to converge, then the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

The Kenward-Roger approximation to estimating the degrees of freedom will be used for tests of fixed effects derived from this model above.

Descriptive summaries of the key secondary endpoints will also be presented.

Adjusted means from this model above will be displayed graphically over time and used to evaluate time of onset of effect. Adjusted means will be calculated from this model 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.

4.2.5.2 Sensitivity analyses

Controlled imputation

Sensitivity analyses of the repeated measures analyses will be performed for all 4 of the continuous key secondary endpoints using controlled sequential multiple imputation methods based on pattern mixture models. Subjects with missing baseline data will be excluded from these analyses.

Although death is not the source of missing data, imputation (MAR and DRMI) will still be performed to assess the impact of no data after death in the primary analysis. Given the

expectation that very few deaths (if any) would be observed in this study, the impact is expected to be minimal.

The multiple imputations will be done in 2 steps:

i. The non-monotone (intermediate visits) missing values will be imputed first, assuming MAR (the Markov chain Monte Carlo [MCMC] method will be used to partially impute the data using SAS PROC MI).
ii. Then, the remaining monotone missing values at each visit will be imputed using the sequential regression method (using the MONOTONE REG option in PROC MI). At each iteration, missing values will be imputed sequentially, one time-point at a time.

In Step (i) 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.

The sequential monotone regression method in Step (ii) is achieved by only including 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.

Different assumptions will be made to impute the monotone missing data:

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

- DRMI (MNAR): Missing data will be imputed differently depending on the reason for dropout in the tezepelumab group. Missing data for subjects in the tezepelumab group who dropped out for a treatment-related reason (assumed) will be imputed assuming the subject's whole distribution, both pre-withdrawal and post-withdrawal, is the same as the placebo group (the "copy reference" approach), whereas the remaining subjects will be imputed assuming MAR.

  Table 7 summarises how subjects withdrawing from study in the tezepelumab group will be handled in the DRMI analyses.

  In the DRMI analyses, to impute missing values at time *t* for subjects in the tezepelumab group who withdrew from the study for treatment-related reasons, 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.

In the DRMI analyses, to impute missing values at time *t* for all placebo subjects and tezepelumab subjects who withdrew from study for reasons unrelated to treatment, the imputations are performed assuming MAR, i.e., using an imputation model which uses subjects who had observed data at time *t* within the respective treatment group. If a negative value is imputed at time *t*, then it will be replaced with a zero value.

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. These same random seeds will be used for the multiple imputation analyses of all 4 key secondary endpoints.

The imputation models will use absolute values of the relevant endpoint (including the baseline value). Change from baseline will then be calculated in imputed datasets. The imputation model will include the same baseline covariates as used in the main analysis model (i.e. those specified in Section 4.2.5.1).

Each of the imputed datasets will be analysed using the same repeated measures model specified in Section 4.2.5.1. An exception is that only the compound symmetry covariance will be assumed (no further covariance investigation) in the sensitivity analyses for all key secondary endpoints. The results from the analysis on each imputed dataset will be combined across imputations in a way which appropriately accounts for within-imputation and between-imputation variance (using the SAS procedure PROC MIANALYZE).

4.2.5.3 Supplementary analyses

The main analyses 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. A compound symmetry covariance will be assumed.

4.2.5.4 Supporting analyses

The analysis of AQLQ(S)+12 total score change from baseline will be repeated for change from baseline in each of the 4 AQLQ(S)+12 domain scores using a similar repeated measures model specified in Section 4.2.5.1.

The analysis of ACQ-6 score change from baseline will be repeated for change from baseline in each of the 6 individual ACQ-6 items using a similar repeated measures model specified in Section 4.2.5.1.

As further supportive analyses to the analyses of change from baseline in ACQ-6, AQLQ(S)+12 and weekly mean daily ASD, responders/non-responders will be summarised descriptively and analysed using a generalised linear model for repeated measures, using a logit link function. In this model, inference will be based on generalised estimating equations

(GEEs) using the method of Liang and Zeger (1986). The response variable in the model will be the binary responder status at each scheduled post-randomisation visit up to and including Week 52, irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region (China or non-China) 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. An unstructured working correlation matrix will be used, along with empirically corrected standard errors. Other working correlation structures may be explored in the scenario of non-converging. For the ASD responder endpoint, each of the 52 weeks used for weekly mean calculation will replace visit in the above model specification.

Only the first (responder/non-responder) ACQ-6 and AQLQ(S)+12 definitions in Section 3.2.3.3 will be analysed using the repeated measures GEE analysis. The other categorical definitions in this section will be summarised descriptively only.

Change from baseline in the percentage of asthma symptomatic days (as defined in Section 3.2.3.5) will be summarised for the planned treatment period for each post-baseline week using descriptive statistics.

As further supportive analysis to the analysis of change from baseline in weekly mean daily ASD score, the main analysis of ASD described in Section 4.2.5.1 will be repeated for changes from baseline in weekly mean daytime and night-time ASD scores using a similar repeated measures model specified in Section 4.2.5.1. Similar descriptive summaries will also be produced.

As further supportive analysis to the analysis of change from baseline in weekly mean daily ASD score, the main analysis of ASD described in Section 4.2.5.1 will be repeated for changes from baseline in weekly mean ASD individual symptom scores (see Section 3.2.3.6) using a similar repeated measures model specified in Section 4.2.5.1. Similar descriptive summaries will also be produced.

For the analyses of other secondary endpoints using similar repeated measures models specified in Section 4.2.5.1, the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

4.2.5.5 Assessing efficacy across phenotypes and other baseline characteristics

Efficacy for the key secondary endpoints will be evaluated separately for biomarkers of interest (which comprises an evaluation of both categorical subgroups and the continuous biomarker variable), and other exploratory variables (which comprises an evaluation of categorical subgroups only).

The same variables will be evaluated for consistency of effect for each of the 4 key secondary endpoints (changes from baseline to Week 52 for each of pre-BD FEV_1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean daily ASD score).

Descriptive summaries of the key secondary endpoints will be presented for the specified categorical variables below, irrespective of how few subjects there are in any particular subgroups. For model-based analyses, if any of the subgroups have fewer than 10 subjects in one or both treatment groups (with data at any post-baseline time point, not necessarily at Week 52), 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.

Biomarkers of interest

Descriptive summaries of each of the key secondary endpoints by treatment group will be produced for each of the following categorical variables:

- Baseline eosinophils group: <300/ µ L, ⩾300/ µ L
- Baseline eosinophils group: <150/ µ L, 150-<300/ µ L, 300-<450/ µ L, ≥450/ µ L
- Baseline eosinophils group: <150/ µ L, ⩾150/ µ L
- Baseline FENO group: <25ppb, ≥25ppb
- Baseline FENO group: <25ppb, 25-<50ppb, ≥50ppb

A similar repeated measures model specified in Section 4.2.5.1 will be fitted as for the key secondary endpoints for each of the above variables in turn, with additional factors for the subgroup variable and the treatment by visit by subgroup interaction (as well as lower order interaction terms including these factors). This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories at Week 52, which will be tabulated and also summarised graphically using a forest plot. The overall treatment effect at Week 52 will be displayed on the forest plot as well.

For the ASD endpoint, each of the 52 weeks used for weekly mean calculation will replace visit in the above model specification.

A p-value for the treatment by subgroup interaction at Week 52 will not be presented for each of these models due to the various difficulties in interpretation.

For the FEV_1 endpoint only, adjusted means from the above model will additionally be summarised graphically over time to evaluate time of onset of effect within each biomarker subgroup category (baseline eosinophils <300/ µ L, ⩾300/ µ L; baseline FENO group: <25ppb, ≥25ppb).

Any unexpected observed pattern may also be further explored using resampling techniques, where null hypothesis data will be generated (in many iterations) to assess the probability of

seeing a pattern as strong (or stronger) by chance only; the null hypothesis will correspond to keeping the main effects intact whilst breaking any potential predictive property of the biomarkers.

A LOESS plot will be produced for each of the continuous biomarker variables (baseline eosinophils (cells/μL), baseline FENO (ppb) and baseline total serum IgE (IU/mL)), for each of the key secondary endpoints.

Other exploratory variables

Descriptive summaries of each of the key secondary endpoints by treatment group will be produced for each of the following categorical variables:

- ICS dose at study entry: medium, high
- Age category: ⩾18 to <65, ⩾65
- Gender: Male, Female
- Exacerbations in the year before study: ⩽2 exacerbations, >2 exacerbations
- OCS at baseline: present, absent
- Baseline BMI: <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2
- Region: China, non-China

A similar repeated measures model specified in Section 4.2.5.1 will be fitted as for the key secondary endpoints for each of the above variables in turn, with additional factors for the subgroup variable (where not already included) and the treatment by visit by subgroup interaction (as well as lower order interaction terms including these factors). This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories at Week 52, which will be tabulated and also summarised graphically using a forest plot. The overall treatment effect at Week 52 will be displayed on the forest plot as well.

For the ASD endpoint, each of the 52 weeks used for weekly mean calculation will replace visit in the above model specification.

A p-value for the treatment by subgroup interaction at Week 52 will not be presented for each of these models due to the various difficulties in interpretation.

For the analyses of other secondary and exploratory endpoints using similar repeated measures models specified in Section 4.2.5.1, where the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

4.2.6 Other secondary endpoints

Annualised rates for supporting exacerbation endpoints will be summarised and analysed as described in Section 3.2.4.1.

Other binary endpoints will be summarised descriptively and analysed using a logistic regression model with factors which will include treatment and region (China or non-China). Baseline of the corresponding endpoint will also be included in the model (where relevant) as a continuous linear covariate. For the binary endpoints defined using absence of exacerbations, the logistic regression model will also include a factor for history of exacerbations (<=2 or >2 in previous 12 months), similarly to the primary analysis in Section 4.2.4.1.

The proportion of subjects who had no asthma exacerbations during the planned treatment period will be summarised descriptively by:

- Exacerbations in the year before study: ⩽2 exacerbations, >2 exacerbations
- Baseline eosinophils group: <300/ μ L, ⩾300/ μ L

A similar logistic regression model will be fitted, for each of these two variables in turn, to this endpoint as above, with additional factors for the subgroup (where not already included) and the treatment by subgroup interaction. This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories.

Other continuous endpoints will be summarised descriptively and analysed using a repeated measures model under a MAR assumption analogous to that specified for key secondary endpoints in Section 4.2.5.1. 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.

The following is proposed for the other continuous secondary endpoints:

- Change from baseline in biomarkers (FENO (ppb), eosinophils (10**9/L and Cells/μL) and total serum IgE (mg/L and IU/mL)) analysed using a repeated measures model specified in Section 4.2.5.1 and summarised descriptively. Eosinophil (10**9/L) and total serum IgE (mg/L) data will also be included in the summaries of laboratory data.
- Change from baseline in weekly mean daily rescue medication use, night-time awakenings, morning home-based PEF and evening home-based PEF analysed using a repeated measures model specified in Section 4.2.5.1; any other eDiary variables only summarised descriptively.
- All HRU items defined in Section 3.2.4.5 only summarised descriptively.

- Change from baseline in EQ-5D-5L VAS and health state valuation index analysed using a repeated measures model specified in Section 4.2.5.1; other EQ-5D-5L dimensions only summarised descriptively.

For the analyses of other secondary endpoints using similar repeated measures models specified in Section 4.2.5.1, only the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

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 (China or non-China) 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 3.2.1, 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.

Time to first asthma exacerbation due to hospitalisations or ER visits will be analysed similarly to time to first asthma exacerbation (all types).

Time to first asthma exacerbation (all types) will also be summarised using Kaplan-Meier estimates separately for subjects within each baseline eosinophils group (<300/ μL, ⩾300/ μL). A similar Cox proportional hazards model will be fitted to this endpoint as above, with additional factors for the subgroup and the treatment by subgroup interaction. This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories. A figure will be produced to summarise the cumulative number of asthma exacerbations over time.

Sensitivity and subgroup analyses will not be performed on other secondary endpoints, except where specified above.

4.2.7 Exploratory endpoints

Change from baseline in total SGRQ score and the 3 domain scores analysed using a repeated measured model specified in Section 4.2.5.1 and summarised descriptively; subjects with SGRQ response analysed using the repeated measures GEE analysis for binary endpoint and summarised descriptively; subjects with SGRQ deterioration analysed descriptively only. Note that in the repeated measured model, the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

Analyses of other exploratory endpoints will be performed after final DBL, see Section 4.2.10.

Note that evaluation of the exploratory onset of effect objective does not require any new analysis here. For this purpose, adjusted means will be extracted at each time point from the repeated measures analyses of the relevant endpoints as specified in Section 4.2.5.1 and Section 4.2.6 and summarised graphically.

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)

AEs will be summarised separately for the on-treatment and on-study periods as defined in Section 3.1.4 unless stated otherwise. All AE summaries will be presented by treatment group. AEs occurring during the screening/run-in period, or occurring post-treatment/follow-up period will be listed, but not summarised separately.

An overall summary table will be produced showing the number and percentage of subjects with at least one AE in each of the following categories: any AEs, SAEs, AEs with a fatal outcome, AEs leading to discontinuation of IP (DAEs), possibly related AEs and possibly related SAEs.

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
- DAEs
- DAEs causally related to 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 addition, each AESI category will be summarised by causality for the on-study period.

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

- All AEs
- Each AESI separately

In these summaries, the exposure adjusted incidence rates will be defined for each treatment group as the number of subjects in that treatment group reporting the AE divided by the total subject-years exposure for that treatment group, the latter as defined in Section 3.3.1. Rates will be reported as events per 100 subject-years. For on-study summaries, exposure for each treatment group will be the total duration of the on-study period, as defined in Section 3.1.4.

Events submitted to the independent adjudication committee for adjudication (myocardial infarction, stroke, malignancy, serious cardiac event, death) will be summarised by treatment group respectively. Events submitted for MACE adjudication (including stroke, myocardial infarction and all deaths) will be summarised separately.

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 3.1.4. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

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

Shift plots showing each individual subject's laboratory value at baseline and at maximum/minimum 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 3.1.4.

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 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 3.1.4. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

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

Shift tables will be produced using all data for the on-study period, as defined in Section 3.1.4.

4.2.8.4 12-lead electrocardiogram (ECG)

Continuous 12-lead 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 3.1.4. 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 Fridericia corrected QT (QTcF) 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.

4.2.9 Pharmacokinetics (PK) and immunogenicity

4.2.9.1 Analysis of PK

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, 24, 52, 64 and at the premature IP discontinuation visit where appropriate. Data will be assigned to weeks based on the visit windows defined in Section 3.1.5. In addition, the following criteria will apply for data to be included in the summary table:

- Only pre-dose samples at week 0.
- Only pre-dose samples at week 24 that were also taken between $\geqslant$ 21 and $\leqslant$ 35 days post the previous dose.
- Only samples at week 52 that were also taken between $\geqslant$ 21 and $\leqslant$ 35 days post the previous dose.
- All samples at week 64 that were taken within the visit window defined in Section 3.1.5.

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, ADA negative), where treatment emergent for ADA is defined below in Section 4.2.9.2.

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 and will be performed separately for participants from China and participants outside of China given the immunogenicity samples analysed at different central laboratories.

The number and percentage 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, 1st quartile, 3rd quartile and range of the maximum ADA titres by treatment group and visit, where applicable, 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 the 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 data 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 having 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 either treatment induced ADA or 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 time point.

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

nAb evaluations will be conducted on confirmed ADA positive samples. The number and proportion of subjects who are nAb positive at any time will be evaluated.

If appropriate (i.e., ≥10 subjects with treatment emergent ADA positive in Tezepelumab treatment group, regardless of placebo status), the association of ADA status across the study

with the primary and key secondary efficacy endpoints, biomarkers and AEs/SAEs may be evaluated.

4.2.10 Analyses outside clinical study report

4.2.10.1 Medication

The total number of days of systemic corticosteroid treatment associated with asthma exacerbations per patient from the date of first dose of IP up to Week 52 will be summarised.

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

Separate tables will be presented for the allowed prior medications, the allowed concomitant medications during post-treatment/follow-up period, and the allowed prior biologics. The medication categories are defined in Section 3.1.6. The allowed medications will be defined following a physician review (prior to the primary database lock) of the unique combinations of ATC code classifications and generic terms captured.

4.2.10.2 Other secondary efficacy endpoints

The proportion of subjects who had no asthma exacerbations associated with hospitalisation or ER visit during the planned treatment period will be summarised descriptively and analysed using a similar logistic regression model as for the proportion of subjects who had no asthma exacerbations during the planned treatment period specified in Section 4.2.6.

Change from baseline in pre-BD $FEF_{25-75\%}$ analysed using a repeated measures model specified in Section 4.2.5.1 and summarised descriptively; other pre-BD clinic visit spirometry only summarised descriptively.

Change from baseline in weekly mean total daily asthma symptom score analysed using a repeated measures model specified in Section 4.2.5.1 and summarised descriptively; weekly mean daytime and night-time asthma symptom scores only summarised descriptively.

For the analyses of secondary endpoints using similar repeated measures models specified in Section 4.2.5.1, only the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

As a supportive analysis to the analysis of change from baseline in ACQ-6, the main analysis of ACQ-6 described in Section 4.2.5.1 will be repeated for change from baseline in ACQ-5 and ACQ-7 scores using a similar repeated measures model specified in Section 4.2.5.1. A compound symmetry covariance will be used. Similar descriptive and graphical summaries will also be produced.

4.2.10.3 Exploratory efficacy endpoints

All continuous exploratory endpoints will be summarised descriptively and analysed under a MAR assumption using a repeated measures model analogous to that specified for key secondary endpoints in Section 4.2.5.1. A compound symmetry covariance will be assumed.

The following is proposed for the exploratory endpoints:

- Change from baseline in post-BD FEV_1 and post-BD $FEF_{25-75\%}$ analysed using a repeated measures model specified in Section 4.2.5.1 and summarised descriptively; other post-BD clinic visit spirometry only summarised descriptively.
- Change from baseline in total SNOT-22 score only summarised descriptively for subjects who had nasal polyps in the 2 years before randomisation and for all subjects in FAS with SNOT-22 data recorded.

Note that evaluation of the exploratory onset of effect objective does not require any new analysis here. For this purpose, adjusted means will be extracted at each time point from the repeated measures analyses of the relevant endpoints as specified in Section 4.2.5.1 and Section 4.2.6 and summarised graphically.

Change from baseline in total SGRQ score will be summarised descriptively by:

- Baseline eosinophils group: <300/ µ L, ⩾300/ µ L
- Baseline FENO group: <25ppb, ≥25ppb

A similar repeated measures model specified in Section 4.2.5.1 will be fitted for total SGRQ score, for each of the above variables in turn, with additional factors for the subgroup variable and the treatment by visit by subgroup interaction (as well as lower order interaction terms including these factors). This model will be used to estimate the treatment effect and its 95% CI within each of the subgroup categories at Week 52.

For the analyses of other exploratory endpoints using similar repeated measures models specified in Section 4.2.5.1, only the compound symmetry covariance structure will be used and no further covariance structures will be investigated.

Annualised CompEx rate in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model, similarly to the primary analysis in Section 4.2.4.1. The response variable in the model will be the number of CompEx events experienced by a subject over the 52-week planned treatment period (or shorter duration if not followed up for the full 52 weeks). Treatment, region (China or non-China) 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 a CompEx event 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 a CompEx event and the 7 days following a CompEx event in which a new event

cannot occur, will not be included in the calculation of time at risk for exacerbation. For all further derivation details, see Section 3.2.5.4.

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

Sensitivity and subgroup analyses will not be performed on exploratory endpoints, except where specified above.

4.2.11 China subpopulation analyses

China subpopulation analyses will be performed using the same methodology as for the overall study population. The China subpopulation includes all Chinese subjects recruited in the study centres in mainland China. The China subpopulation analyses were pre-specified before primary DBL.

Analyses of the primary endpoint (AAER), key secondary endpoints (pre-BD FEV_1, AQLQ(S)+12, ACQ-6, ASD) and other selected efficacy secondary endpoints will be repeated for China subpopulation. Selected subgroup analyses will be repeated for China subpopulation. Sensitivity analyses will not be repeated for China subpopulation. All statistical analyses for China subpopulation will be considered exploratory. No adjustment for multiplicity will be made and so the multiple testing procedure as described in Section 4.1.2 will not be followed for China subpopulation analyses. Region (China or non-China) will not be adjusted in the statistical model as all patients are from China.

Safety and PK analyses as outlined in Section 4.2.8 and 4.2.9.1 will be repeated for the China subpopulation as appropriate.

5. INTERIM ANALYSES

No interim analyses are planned in this trial.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The number of asthma symptomatic days has been included as an exploratory endpoint in Section 3.2.3.5, but is not included as an exploratory endpoint in the protocol v7.0.

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 3.2.4.3, but is not included as an exploratory endpoint in the protocol v7.0. The daytime and night-time scores from this assessment have also been included.

The protocol v7.0 specifies that serum trough concentrations will be the PK endpoint. However data from follow-up visits (Week 64) will be included in the analyses and is referred to as serum concentration not trough concentration. A table footnote has been added in Section 1.1.3 for clarification, and the text in Section 3.4 and Section 4.2.9.1 has been updated to reflect this.

The protocol v7.0 does not specify that all immunogenicity analyses will be performed separately for China and non-China given the immunogenicity samples analysed at different central laboratories, while this has been specified in Section 4.2.9.2.

The protocol v7.0 states that the analysis of change from baseline in ACQ-6, the main ACQ-6 analysis will be repeated for change from baseline in ACQ-5 and ACQ-7 scores using a similar repeated measures model as a supportive analysis. However, this supporting analysis is moved to analysis outside of CSR scope (Section 4.2.10).

7. REFERENCES

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8. APPENDIX

8.1 Adverse events of special interest (AESIs)

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 the primary database lock and provided together with the study datasets at the time of submission.

8.1.1 Serious hypersensitivity reactions

Serious hypersensitivity reactions are defined as a combination of anaphylactic reactions (used with a time restriction) and events meeting regulatory serious criteria (see CSP v6 Appendix A1) within the 'Hypersensitivity' narrow SMQ (no time restriction).

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

8.1.1.1 Anaphylactic reactions

- Potential anaphylactic reactions will be defined on the basis of Sampson's criteria (see Sampson et al., 2006). These will be identified using a modified Standardised MedDRA Query (SMQ), with additional constraints on the timing of the AE onset date relative to the timing of the injection (within 3 days).

- 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.

8.1.1.2 Hypersensitivity

- Events meeting regulatory serious criteria (see CSP v7 Appendix A1) within the 'Hypersensitivity' narrow SMQ.

8.1.2 Malignancy

Malignancy will be defined on the basis of an SMQ, using 'SMQ: Malignant or unspecified tumours'.

8.1.3 Helminth infections

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

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

8.1.4 Serious infections

Serious infections are defined as events meeting regulatory serious criteria (see CSP v6 Appendix A1) within the 'Infections and infestations' SOC.

8.1.5 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ, using 'SMQ: Guillain Barre syndrome'.

8.1.6 Serious cardiac events

Serious cardiac events are defined as events meeting regulatory serious criteria (see CSP v7 Appendix A1) within the 'Cardiac disorders' SOC.

8.2 OCS conversion factors for prednisone equivalents

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

Table 8 Estimated OCS dose therapy equivalence

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

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

8.3 Maintenance therapy equivalence table

Total daily ICS dose will be converted to a medium/high category using the following table:

Table 9 Estimated daily doses for inhaled corticosteroids

Asthma Therapy	Total Daily Dose (µg/day)	
Inhaled Corticosteroid	**Medium**	**High**
Beclomethasone dipropionate (non HFA)	1000	>1000
Beclomethasone dipropionate (HFA)	400	>400
Ciclesonide	320	>320
Triamcinolone acetonide	2000	>2000
Flunisolide	2000	>2000

Fluticasone furoate (e.g. Arnuity® Ellipta®)	NA	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®)	NA	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.

8.4 Analyses to assess the impact of the COVID-19 pandemic

Additional analyses and summaries will be produced to assess the impact of the COVID-19 pandemic on the primary results. The analyses and summaries are detailed below, referencing the section of this SAP to which they relate to.

COVID-19 phases (pre- / during- / post-)

The start date of COVID-19 pandemic will be defined at a country level: 29th January 2020 (the date China declared COVID-19 to be a national public health crisis, i.e., significant emergent public health grade one response started across China provinces) for China, 11th March 2020 (the date WHO declared COVID-19 to be a pandemic) for non-China countries.

The end date of COVID-19 pandemic may be defined at a site / country / study level and will be defined in a future version of this Appendix, if applicable.

Data recorded before the start date will be *pre-pandemic*. Data recorded on or after the end date (if defined) will be *post-pandemic.* Data recorded on or after the start date and before the end date (if defined) will be *during-pandemic*. If the end date is not defined for a subject (at the relevant site / country level; or at the study level), all data recorded on or after the start date will be *during-pandemic* for that subject.

If the end date is not defined for China, all China data will be classified as *during-pandemic*, given the first Chinese subject enrolment was in July 2020.

Violations and deviations

All important PDs will be summarised and listed together, including COVID-19-related and non-COVID-19-related important PDs (see Section 2.2). An additional summary will present COVID-19-related important PDs by treatment group, for the FAS.

COVID-19-related study disruptions

A COVID-19-related study disruption is any important change in the study conduct or data collection due to the COVID-19 pandemic. COVID-19-related study disruptions may include, but not necessarily be limited to:

- Changes to visit schedules, missed visits, changes to visit procedures;
- Discontinuation of IP, missed IP, changes to IP administration;
- Discontinuation of study.

An additional table will summarise all COVID-19-related study disruptions by treatment group for the FAS. The number and percentage of subjects with at least one COVID-19-related study disruption will be reported.

The number and percentage of subjects randomised pre-pandemic will be reported, along with the number and percentage of subjects randomised post the start date of COVID-19 pandemic. If applicable, the number and percentage of subjects randomised post-pandemic will be reported.

Total pre-pandemic, during-pandemic and, if applicable, post-pandemic follow-up times will be presented in total subject-years and also as proportions of total follow-up time, as an indication of the proportion of study time potentially affected by COVID-19.

The number and percentage of subjects who missed at least one IP dose, the number and percentage of subjects missing 1, 2, 3, 4, … doses, and the number and percentage of subjects with 2, 3, 4, … consecutive missed doses due to COVID-19 will be presented.

The number and percentage of subjects with at least one missed scheduled visit, delayed on-site visit or changed format of scheduled visit, will be summarised by treatment group. Impacted visits will be classified on “VISIT” eCRF page as “Remote – Audio”, “Remote – Video”, “On-Site Visit”, “Home Visit”, “Other” and “Not done”.

The number of subjects discontinuing IP or withdrawing from the study due to COVID-19 will also be summarised by treatment group.

Analyses of the primary endpoint

An additional sensitivity analysis of the primary endpoint will be carried out to compare exacerbation rates in the tezepelumab group with those in the placebo group during the pre-pandemic phase. The analysis will use pre-pandemic data only, i.e., data over the 52-week exacerbation follow-up period up to and including the day prior to the start date of pandemic.

The comparison will use all observed data in this pre-pandemic period regardless of adherence to randomised treatment or the use of an alternative treatment**.**

An additional sensitivity analysis will compare annualised exacerbation rates in the tezepelumab group with those in the placebo group using during-pandemic data only. This analysis will use all observed data from the start date of pandemic until the earlier of: the end of the exacerbation follow-up period (see Section 3.2.1.1); or the day prior to the end date of pandemic (if defined).

All these sensitivity analyses will use a similar negative binomial model as specified for the primary analysis (see Section 4.2.4.1). The response variable will be the number of exacerbations experienced by a subject during the follow-up for exacerbations in the specific COVID-19 phase. The logarithm of the subject's corresponding time at risk in the specific COVID-19 phase will be used as an offset variable in the model. The model for pre-pandemic phase will include covariates of treatment and history of exacerbations (<=2 or >2 in previous 12 months); the model for during-pandemic phase will include covariates of treatment, region (China or non-China), history of exacerbations (<=2 or >2 in previous 12 months).

AEs

All AE-related analyses described below will be based on the safety analysis set using the on-treatment period (see Section 4.2.8.1).

The overall AE summary table (AEs in any category reported) will be repeated by pandemic phase: pre-pandemic, during-pandemic and post-pandemic (if applicable). Categories will include: any AEs, SAEs, AEs with a fatal outcome, DAEs, possibly related AEs and possibly related SAEs.

The AE adjudication listing will also show the adjudicated relationship to COVID-19.

8.5 Efficacy estimand

Estimand	Estimand attributes			Analysis (SAP section)
	Treatment / Population	**Endpoint / Population level summary**	**Intercurrent event (strategy in main estimation)**	
Primary objective: To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult subjects with severe uncontrolled asthma compared with placebo				
Primary estimand: Ratio of exacerbation rate between tezepelumab and placebo in adult patients with severe uncontrolled asthma, regardless of whether patients discontinue study treatment, initiate new treatment or change background treatment	Treatment with tezepelumab versus placebo, as add-on to standard of care / Adult patients with severe uncontrolled asthma and a history of asthma exacerbations receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS	AAER / AAER ratio of Tezepelumab versus placebo over 52 weeks	• Use of alternative treatment (Treatment policy strategy) • Discontinuation of study treatment (Treatment policy strategy) • Change in background treatment (Treatment policy strategy) • Patient death (While alive strategy) • COVID-19 pandemic (Treatment policy strategy)	• Main estimation (Section 4.2.4.1): The primary analysis will compare AAER over 52 weeks between treatment groups using a negative binomial model, including all available data. • Sensitivity analyses for missing data (Section 4.2.4.2): Controlled multiple imputation analyses will be performed under MAR and DRMI (MNAR) assumptions respectively. Tipping point analyses will be performed using similar multiple imputation method. • Sensitivity analyses for pandemic impact (Appendix 8.4): Similar negative binomial models as for the primary analysis will be carried out separately for the pre-pandemic data and during-pandemic data.
Four key secondary objectives: (1) To assess the effect of 210 mg tezepelumab SC Q4W on pulmonary function compared with placebo; (2) To assess the effect of 210 mg tezepelumab SC Q4W on health status/health related quality of life compared with placebo;(3) To assess the effect of 210 mg				

Estimand	Estimand attributes			Analysis (SAP section)
	Treatment / Population	**Endpoint / Population level summary**	**Intercurrent event (strategy in main estimation)**	
tezepelumab SC Q4W on asthma control compared with placebo; (4) To assess the effect of 210 mg tezepelumab SC Q4W on asthma symptoms compared with placebo.				
Secondary estimand: Difference in change from baseline between tezepelumab and placebo in adult patients with severe uncontrolled asthma, regardless of whether patients discontinue study treatment, initiate new treatment or change background treatment	Treatment with tezepelumab versus placebo, as add-on to standard of care / Adult patients with severe uncontrolled asthma and a history of asthma exacerbations receiving medium or high dose ICS plus at least one additional asthma controller medication with or without OCS	(1) Change from baseline in Pre-BD FEV_1 / Mean difference vs placebo at Week 52 (2) Change from baseline in AQLQ(S)+12 total score / Mean difference vs placebo at Week 52 (3) Change from baseline in ACQ-6 / Mean difference vs placebo at Week 52 (4) Change from baseline in weekly mean daily ASD score / Mean difference vs placebo at Week 52	• Use of alternative treatment (Treatment policy strategy) • Discontinuation of study treatment (Treatment policy strategy) • Change in background treatment (Treatment policy strategy) • Patient death (While alive strategy) • COVID-19 pandemic (Treatment policy strategy)	• Main estimation (Section 4.2.5.1): The primary analysis will compare mean change from baseline at week 52 between treatment groups using a linear model for repeated measures, including all available data. • Sensitivity analyses for missing data (Section 4.2.5.2): Sensitivity analyses will be performed for all 4 of the continuous key secondary endpoints using controlled sequential multiple imputation methods based on the pattern mixture models, under MAR and DRMI (MNAR) assumptions respectively.

AAER=Annualized Asthma Exacerbation Rate; ACQ-6=Asthma Control Questionnaire-6; AQLQ(S)+12=Standardised Asthma Quality of Life Questionnaire for 12 Years and Older; ASD=Asthma Symptom Diary; BD=Bronchodilator; DRMI=Dropout Reason-based Multiple Imputation; FEV_1=Forced Expiratory Volume in 1 second; MAR=Missing At Random; MNAR=Missing Not At Random.