AstraZeneca

Statistical Analysis Plan

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

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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
ATS/ERS	American Thoracic Society/European Respiratory Society
AZ	AstraZeneca
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood Pressure
CGI-C	Clinician Global Impression of Change
CompEx	Composite Endpoint for Exacerbations
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTD	Common Technical Document
DAE	Adverse Event Leading to Discontinuation of Investigational Product
DBL	Database Lock
DNA	Deoxyribonucleic Acid
DRMI	Dropout Reason-based Multiple Imputation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study

Abbreviation or special term	Explanation
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
$FEF_{25-75\%}$	Forced Expiratory Flow over 25-75% of the vital capacity
FEIA	Fluorescent Enzyme Immunoassay
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
FWER	Familywise Error rate
GCP	Good Clinical Practice
GEE	Generalised Estimating Equation
GI	Gastrointestinal
HRQoL	Health Related Quality of Life
HRU	Health Resource Utilization
ICS	Inhaled Corticosteroids
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Investigational Product
IPD	Investigational Product Discontinuation
ITT	Intent-to-Treat
IXRS	Interactive Voice/Web Response System
L	Litre
LABA	Long-Acting Beta Agonist
LLOQ	Lower Limit of Quantification
LLT	Lower Level Term
LOESS	Locally Estimated Scatterplot Smoothing
MACE	Major Adverse Cardiac Events
MAR	Missing At Random

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
N/A	Not Applicable
nAb	Neutralizing Antibodies
NB	Negative Binomial
NC	Not Calculable
NQ	Non-quantifiable
OCS	Oral Corticosteroids
PD	Protocol Deviation
PEF	Peak Expiratory Flow
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PT	Preferred Term
Q4W	Every 4 Weeks
QTc	Corrected QT Interval
RNA	Ribonucleic Acid
SABA	Short-Acting Beta Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
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)
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
TBL	Total Bilirubin
Th1	CD4+ T Helper Type 1

Abbreviation or special term	Explanation
Th2	CD4+ T Helper Type 2
Th17	CD4+ T Helper Type 17
UC	Urgent Care
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
VAS	Visual Analog Scale
WHO	World Health Organisation
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
N/A	28-Jun-18	Initially Approved SAP	Yes	Initial SAP. In line with CSP version 3.0 (16 March 2018).
Primary or secondary endpoints	17-May-19	Sections 1.1.3 and 3.2.4.1: Supportive endpoint to the secondary endpoint has been updated from proportion of subjects with ≥1 asthma exacerbation to proportion of subjects who did not experience an asthma exacerbation over 52 weeks.	No	The endpoint was updated to align with the question of interest.
Primary or secondary endpoints	17-May-19	Sections 3.2.3.7 and 4.2.5.4: Additional endpoint for Asthma Symptom Diary (ASD) responders added.	N/A	Added to support the analysis of change from baseline in ASD.
Primary or secondary endpoints	14-Sept-20	Section 3.2.1.1: Added reference to the definition in the CSP.	Yes	To provide clarification that the definition of an exacerbation is from the CSP.
Statistical analysis method for the primary or secondary endpoints	17-May-19	Section 4.1.1: Amendment to multiple testing procedure and associated statements.	Yes	To reflect CSP amendment version 4.0 (15 Apr 2019).
Statistical analysis method for the primary or secondary endpoints	17-May-19	Section 4.2.4.2 & 4.2.5.2: Expansion of sections on missing data sensitivity analysis (including the addition of tipping point analysis)	N/A	Following programming reviews and recommendation from FDA.
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.4.1: Changed study discontinuation to study withdrawal.	N/A	Consistency of text.
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.4.1: Definition of treatment policy estimand includes all data in the planned treatment period.	N/A	Provide additional clarification.
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.4.1: Noted that death may also be a source of missing information for the primary analysis.	N/A	Provide additional clarification.
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.4.2: Removed reference to direct likelihood. Included description of the negative binomial distribution and its parameters.	N/A	Provide additional clarification and consistency of approach.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		Added specification of prior distributions. Text added to imputation of missing data for primary endpoint. For the DRMI analysis, subjects who discontinued IP due to lost to follow-up will now be assigned to placebo by default and not tezepelumab. Updated the algorithm so that for subjects with an imputed number of exacerbations after withdrawal, the offset will now exclude the time during any observed exacerbation and the 7 days following.		
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.5.1: Definition of treatment policy estimand includes all data in the planned treatment period..	N/A	Provide additional clarification.
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.5.1: Noted that subjects selecting option 3 for follow-up will be a source of missing information for some of the key secondary analyses in addition to those choosing option 2 having missing pre-BD FEV1.	N/A	Provide additional clarification.
Statistical analysis method for the primary or secondary endpoints	14-Sept-20	Section 4.2.5.2: Text added to imputation of missing data for key secondary endpoints. Notes that subjects with missing baseline data will be excluded from these analyses	N/A	Provide additional clarification.
Derivation of primary or secondary endpoints	14-Sept-20	Sections 1.1.3, 3.2.3.1, 3.2.3.3, 3.2.4.1, 4.2.4.4, 4.2.6: Remove “Urgent Care” from definition of secondary and supportive analyses.	No	Provide clarification that only emergency room visit data is collected in the eCRF.
Derivation of primary or secondary endpoints	14-Sept-20	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 dosing.	N/A	Remove redundant text and simplify section.
Derivation of primary or secondary endpoints	14-Sept-20	Section 3.2.1.1: Time at risk derivation updated to allow the date of last exacerbation status to be considered in derivation and remove the use of available visits prior to Visit 17 in determining the date of last exacerbation assessment.	N/A	Simplify the text.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		The text stating that the date of Visit 17 will be used irrespective of how late this may have occurred in relation to the protocol schedule has also been removed.		
Derivation of primary or secondary endpoints	14-Sept-20	Section 3.2.1.1: Noted the definition of an exacerbation in line with the CSP.	Yes	We have removed urgent care from the definition of supportive analyses, but urgent care is part of the definition used in the start and end dates.
Derivation of primary or secondary endpoints	14-Sept-20	Section 3.2.4.1: Clarification provided for supportive endpoint of proportion of subjects who did not experience an asthma exacerbation.	N/A	Provide additional clarification.
Data presentations	17-May-19	Section 2.2: Categories for grouping important protocol deviations updated	N/A	For consistency with study Protocol Deviations Plan.
Data presentations	17-May-19	Section 3.1.6: Visit windows updated to include bi-weekly windows for EQ-5D-5L and a visit window for variables collected on a sparse CSP schedule	N/A	To allow data to be included in appropriate analysis timepoints.
Data presentations	17-May-19	Section 3.1.7: definition of medications during the post-treatment period updated	N/A	To only include new medication starting during this period.
Data presentations	17-May-19	Section 3.1.8: additional subgroup for FENO added. Clarification of derivation of IgE subgroup. Race subgroup updated to reflect eCRF categories. BMI subgroup updated to reflect general guidelines on BMI categories.	N/A	To clarify subgroup definitions.
Data presentations	17-May-19	Section 4.2.6.5: statistical analysis of the daytime and night-time scores for ASD added.	N/A	Analysis added to support the interpretation of the ASD total score.
Data presentations	17-May-19	Section 4.2.8.1: further summaries of injection site reactions will be provided based on injection site and total doses of IP administered.	N/A	Required for CSR.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	14-Sept-20	Section 2.1.3:Addition of condition that subjects must have at least one sample with detectable drug levels to be included in the PK analysis set.	N/A	Provide additional clarification.
Data presentations	14-Sept-20	Section 2.1.5: Removed text not referring to the on-treatment definition.	N/A	Remove redundant text.
Data presentations	14-Sept-20	Section 2.2: Added the exception that PDs may lead to the exclusion of data for the PK analyses.	N/A	Provide additional clarification
Data presentations	14-Sept-20	Section 3.1.1: Added text clarifying the definition of baseline for the PK data.	N/A	Provide additional clarification
Data presentations	14-Sept-20	Section 3.1.4 updated “Post-treatment” period to “Post-treatment/Follow-up” period and clarified the start date begins after the on-treatment period.	Yes	For consistency with programming reporting requirements and CSP amendment version 5.0 (14 May 2020).
Data presentations	14-Sept-20	Section 3.1.5: Clarified that any listings produced will include all data recorded, removed unnecessary text regarding the 16 week follow-up visit and noted how multiple ADA samples will be handled..	N/A	Provide additional clarification.
Data presentations	14-Sept-20	Section 3.1.5: Updated visit window for week 58.	N/A	In line with new AZ guideline on reporting safety data.
Data presentations	14-Sept-20	Section 3.1.7: Definition of positive IgE panel, seasonal and perennial subgroups added. Removed baseline IgE status allergic/non-allergic as efficacy subgroup and added baseline perennial IgE status. Reference to IgE status updated to “specific IgE status (FEIA)” Text describing baseline IgE status allergic/non-allergic changed to any FEIA positive/all FEIA negative.	N/A	Required for CSR
Data presentations	14-Sept-20	Section 3.1.7: Definition of OCS subgroup changed to OCS at baseline.	N/A	Required for CSR

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Data presentations	14-Sept-20	Section 3.1.7: Changed age categories from adults (>65), adults (≥18 to ≤65) to adults (≥65), adults (≥18 to <65)	N/A	In line with AZ standards.
Data presentations	14-Sept-20	Section 3.1.7: Clarified derivation of biomarker quartiles and baseline status for nasal polyps, chronic sinusitis and rhinitis.	N/A	Provide additional clarification.
Data presentations	14-Sept-20	Sections 3.1.7 and 4.2.9.3: Addition of weight and drug concentration quartiles together with analyses of the primary endpoint and pre-BD FEV1.	N/A	Addition of exposure-response analyses.
Data presentations	14-Sept-20	Sections 3.1.7, 4.2.4.5, 4.2.5.5: Removed CRSwNP as subgroup for efficacy analyses and added new subgroup, nasal polyps in the 2 years before randomisation.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 3.1.8: Details added to derivation of time to last dose of IP.	N/A	To clarify derivation rules.
Data presentations	14-Sept-20	Section 3.1.8: Time to premature study withdrawal for subjects ongoing at primary DBL will be censored at last contact date rather than at Week 52.	N/A	Provides additional information of progress of ongoing subjects.
Data presentations	14-Sept-20	Section 3.2.2.4: Clarification that individual items of ASD will be derived and reporting of data after Week 52	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 3.2.3.1: Clarification that the supporting endpoint in which hospitalisations and ER visits that are adjudicated to be asthma related are added, not adjudicated due to an asthma exacerbation.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Sections 3.2.4.2, 4.2.4.5, 4.2.5.5, 4.2.6: Clarified units to be used for reporting eosinophils and total serum IgE.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 3.2.4.3: “Daily asthma symptom total score” changed to “Total daily asthma symptom	N/A	Provides clarity for TFLs and consistency with other project

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		score", clarified night-time awakenings are those that required rescue medication. Text added to clarify that this is different from the total score derived from the ASD		documents..
Data presentations	14-Sept-20	Section 3.2.4.5: Health care resource utilisation extended to include all data on study and clarified that the unit may be number of times or days, depending on the endpoint.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 3.2.5.2: Clarified that the immunoglobulin endpoints will be derived in the same manner as the laboratory data.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 3.3.2: Addition of study adjusted incidence rate for adverse events.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 3.3.2: Derivation of exposure adjusted incidence rates.	N/A	In line with new AZ guideline on reporting safety data.
Data presentations	14-Sept-20	Section 3.3.4: Values below the Lower Limit of Quantification (LLOQ) will be set to LLOQ, instead of LLOQ/2.	N/A	In line with new AZ guideline on reporting safety data.
Data presentations	14-Sept-20	Section 4.2.1: Added eosinophil subgroups to summaries.	N/A	Required for CSR.
Data presentations	14-Sept-20	Sections 4.2.1, 4.2.2, 4.2.3, 4.2.6, 4.2.8.1 and 4.2.9.2: Added age subgroups at study entry to summaries and analyses.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.2: Added text noting that baseline total daily dose to be displayed will be the categories low/medium/high.	N/A	Provide additional clarification.
Data presentations	14-Sept-20	Section 4.2.2: Added text regarding disallowed medications.	Yes	Provide additional clarification.
Data presentations	14-Sept-20	Section 4.2.4.4: Added analysis of annualised exacerbation rates which consider adjudicated outcomes for exacerbations due to hospitalisations.	N/A	Required for CSR.
Data presentations	14-Sept-20	Sections 4.2.4.5, 4.2.5.5 and 4.2.7: Subgroup changed from baseline IgE status allergic/non-allergic as efficacy subgroup to baseline perennial	N/A	Required for CSR.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		IgE status.		
Data presentations	14-Sept-20	Sections 4.2.4.5 and 4.2.5.5: Subgroup changed from OCS at study entry to OCS at baseline.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.4.5: Removed text regarding bootstrapping.	N/A	To avoid misinterpretation when creating standardised effect plots.
Data presentations	14-Sept-20	Section 4.2.5.3: Changed range of pre-BD FEV1 to be used in tipping point analysis from 0 to 0.3 L in increments of 0.1 mL to 0.1 L.	N/A	Provide additional clarification.
Data presentations	14-Sept-20	Sections 4.2.5.4, 4.2.8.2, 4.2.8.3, 4.2.8.4 and 4.2.9.1: Updated to present visit-based summaries over time using the on-study period instead of the on-treatment period	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.5.5: Removed text stating that the adjusted means from the analysis of FEV1 will be tabulated for the subgroup analyses. These data will only be summarised graphically. Removed text regarding bootstrapping.	N/A	Provide additional clarification and to avoid misinterpretation when creating standardised effect plots.
Data presentations	14-Sept-20	Section 4.2.6: Added a figure summarising the cumulative number of asthma exacerbations.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.6: Noted that eosinophil and total serum IgE will also be included in the summaries of laboratory data.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.6: Removed text stating that separate daytime and night time components of PEF will only be described descriptively.	N/A	Provide additional clarification.
Data presentations	14-Sept-20	Section 4.2.6: Change from baseline in weekly mean total daily asthma symptom score analysed using MMRM and summarised descriptively; weekly mean daytime and night-time asthma symptom scores only summarised descriptively.	N/A	Required for CSR
Data presentations	14-Sept-20	Section 4.2.7: Adjusted means at each timepoint from the MMRM analyses will be summarised	N/A	Provide additional clarification.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
		graphically.		
Data presentations	14-Sept-20	Section 4.2.7: IgA, IgG and IgM data will be included in the summaries of laboratory data.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.7: Removed text regarding summaries of total and specific immunoglobulin endpoints. New text added to describe summaries of serum biomarker available primary DBL.	N/A	Specific IgE data are only available at baseline. Total IgE data are described in Section 4.2.6.
Data presentations	14-Sept-20	Section 4.2.7: SNOT-22 data will be summarised for a) all subjects with SNOT-22 data recorded and b) the subset of subjects who had nasal polyps in the 2 years before randomisation. This subset will also be analysed using an MMRM model.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.8.1: AE summaries for causality and maximum intensity will be reported by PT only and not SOC and PT.	N/A	For consistency with AZ reporting standards.
Data presentations	14-Sept-20	Section 4.2.8.2: All summaries and figures will report laboratory data in SI units.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 4.2.8.2: Removed figure of mean changes from baseline.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 4.2.8.2, 4.3.8.3: Shift tables will not display missing values. Shift plots will not present reference lines for normal ranges.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 4.2.9.1: Added non-treatment-emergent ADA positive.	N/A	Required for CSR.
Data presentations	14-Sept-20	Section 4.2.9.1: Clarified data to be included in the summary of serum tezepelumab concentrations.	N/A	Provides clarity for TFLs.
Data presentations	14-Sept-20	Section 4.2.9.2: Added the association of ADA status with key secondary and biomarker data may be evaluated and clarified only number of ADA positive subjects will be summarised at each visit.	N/A	Required for CSR.

Category: Change refers to	Date	**Description of change**	**In line with the CSP?**	**Rationale**
Data presentations	14-Sept-20	Addition of Appendix 8.4 describing COVID-19 outputs.	N/A	Required for CSR to assess impact of the COVID-19 pandemic.
Other	17-May-19	Reference to DBL updated to primary DBL in the following sections: 2.1.4 and 4.2.2.	Yes	To accommodate a planned additional database lock once the last subject completes treatment phase (week 52).
Other	14-Sept-20	Section 1.1.3, 3.4 & 4.2.9.1: Removed the word trough from the endpoint, serum trough concentrations.	No	To provide additional clarification as not only trough concentrations will be summarised.
Other	14-Sept-20	Section 1.1.3: Clarified the FENO data are the clinic-based measurements.	No	Home-based FENO are also recorded.
Other	14-Sept-20	Section 1.1.3: Clarified weekly mean morning and evening PEF data are the home-based measurements.	No	Clinic based PEF are also recorded.
Other	14-Sept-20	Section 1.1.5 & 3.2.5.2: Exploratory endpoint of total IgE removed	N/A	Already covered in Section 1.1.3 & 3.2.4.2.
Other	14-Sept-20	Sections 1.1.5 and 3.2.5.2: Exploratory endpoint of allergen specific IgE removed	Yes	CSP amendment version 5.0 (14 May 2020).
Other	14-Sept-20	Section 1.1.5: Added endpoint mean difference vs placebo at week 52 for SGRQ.	Yes	Consistency with protocol.
Other	14-Sept-20	Sections 1.1.5, 3.2.5.8, 4.2.4.2: Replaced the word patients with subjects.	Yes	Consistency throughout document.
Other	14-Sept-20	Section 1.2: Text updated to state that the follow-up period may not apply to subjects who participate in the extension study.	Yes	CSP amendment version 5.0 (14 May 2020).
Other	14-Sept-20	Section 2.2: Clarified only not fulfilling key eligibility criteria will be considered important PDs	No	Consistent with Protocol Deviation plan.
Other	14-Sept-20	Sections 3.2.3.5 and 4.2.5.4: Percentage of symptomatic days will be presented instead of non-symptomatic days	N/A	Preference for reporting of endpoint.

Category: Change refers to	Date	**Description of change**	**In line with the CSP?**	**Rationale**
Other	14-Sept-20	Section 3.2.3.6: Means derived for individual symptom scores within the ASD will combine daytime and night-time data and removed text already specified in Section 3.2.2.4.	N/A	Provides clarity for TFLs.
Other	14-Sept-20	Section 3.2.5.1: Added derivation for serum biomarker data.	N/A	Required for CSR.
Other	14-Sept-20	Sections 3.3.2, 4.2.8.3: Treatment-emergent text replaced with "during on-treatment period".	N/A	For consistency with reporting periods.
Other	14-Sept-20	Section 3.3.6: Changed ECG to digital ECG	Yes	Consistency with protocol.
Other	14-Sept-20	Section 6: Removed text regarding the supporting endpoint "proportion of subjects who did not experience an asthma exacerbation over 52 weeks". Additional text added for changes from CSP version 5.0.	Yes	To reflect CSP amendment version 5.0 (14 May 2020).
Other	14-Sept-20	Section 6: Additional text added for changes from CSP version 5.0.	No	Required for CSR.
Other	14-Sept-20	Appendix 8.3: Added to include therapy equivalent table for ICS therapy from CSP with additional note for Budesonide as a metered dose.	Yes	Provides clarity for TFLs.
Other	22-Oct-20	Formatting and links fixed	N/A	No changes to content, however formatting reflecting house style and errors in links resolved.

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5180C00007. The SAP describes the statistical analyses specified in the latest version of the clinical study protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

1.1 Study objectives

1.1.1 Primary objective

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent 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 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 visit or hospitalisation 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 • Clinic based fractional exhaled nitric oxide FENO (ppb) • peripheral blood eosinophils • total serum IgE Outcome measure: Mean difference vs placebo at Week 52
To assess the effect of 210 mg of tezepelumab SC Q4W on other asthma control metrics	Outcome variables: Change from baseline in • weekly mean rescue medication use • weekly mean morning and evening home-based 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.

Objective:	Endpoint/variable:
To assess the effect of 210 mg tezepelumab SC Q4W compared with placebo on health resource utilization and productivity loss due to asthma	Outcome variables: • Asthma specific resource utilization (e.g. unscheduled physician visits, unscheduled phone calls to physicians, use of other asthma medications) • Work Productivity and Activity Impairment (WPAI+CIQ) Questionnaire and Classroom Impairment Questionnaire score Outcome measures: • Difference in number of asthma specific resource utilizations vs placebo over 52 weeks • Difference in WPAI+CIQ score vs placebo at Week 52
To evaluate the pharmacokinetics (PK) and immunogenicity of tezepelumab	PK: Serum concentrations Immunogenicity: Incidence of anti-drug antibodies
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
To assess the effect of 210 mg of tezepelumab SC Q4W on patient (PGI-C and PGI-S) and clinician impression of overall asthma severity (CGI-C)	Outcome variable: Patient Global Impression of Change/Severity (PGI-C, PGI-S) and Clinician Global Impression of Change (CGI-C) Outcome measures: Proportions of responses at Week 52

1.1.4 Safety objectives

Objective:	Endpoint/variable:
To evaluate the safety and tolerability of tezepelumab	Adverse events/serious adverse events Vital signs Clinical chemistry/haematology/urinalysis parameters Digital electrocardiograms

1.1.5 Exploratory objectives

CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI

1.2 Study design

This is a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group study to evaluate the effect of 210 mg of tezepelumab administered Q4W SC in adult and adolescent 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.

The study will randomise approximately 1060 subjects globally in a 1:1 ratio to either:

- Tezepelumab 210mg every 4 weeks (Q4W) by subcutaneous (SC) injection, or
- Placebo Q4W by SC injection.

Approximately 80 adolescents are expected to be included. Randomisation will be stratified by:

- Region [Western Europe plus Australia; South America; North America; Asia Pacific; Central/Eastern Europe; Rest of World], and
- Age group at screening [adult (18-80 years); adolescent (12-17 years)].

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. It may be applied to the adult population instead of the overall population to avoid difficulties with adolescent recruitment, if this becomes necessary. The clinical factors which will be monitored, and the target percentages anticipated to be used for this monitoring, are:

- Exacerbation history in previous 12 months (at least 40% subjects with ≥3 exacerbations; at most 60% subjects with exactly 2 exacerbations)
- Background ICS dose level (at most 20% subjects on medium ICS dose; at least 80% subjects on high ICS dose)
- Eosinophil level at screening (50% subjects with <300 eosinophils/μL; 50% 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 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. The follow-up period may not apply to subjects who participate in the extension study. Any data collected after a subject is enrolled in the extension study will not be included in the analyses described in this SAP.

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.

1.3 Number of subjects

Approximately 1060 subjects will be randomly assigned to study treatment using 1:1 allocation between the two treatments. Since the primary analysis of the primary endpoint will include all available data, including after treatment discontinuation, no need is envisaged to adjust the number of subjects planned to be randomised in order to obtain a number of evaluable subjects.

With 530 subjects per treatment group it is estimated that, using the multiple testing procedure described in Section 4.1.2 with an overall Type 1 error control at α=0.05 and a Type 1 error control for the primary endpoint at α=0.01, the power for the primary and the key secondary endpoints will be at least 90%. The Type 1 error control at α=0.01 for the primary endpoint is chosen to further ensure statistically persuasive evidence.

For the primary endpoint, assuming a placebo rate of 0.9 per year, a shape parameter of 2.4 (overdispersion), and a dropout rate of 10% (assumed uniform over the study), there will be at least 99% power to detect a rate reduction of 50% at a 2-sided significance level of 1%. 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 27%.

For AAER in subjects with baseline eosinophils < 300/μL, assuming a placebo rate of 0.6 and assuming that half of subjects will be in this subgroup (i.e. 265 subjects per treatment group), there will be 94% power to detect a rate reduction of 50% at a 2-sided significance level of 5%, with the same shape parameter and dropout assumptions as above.

For each of the following four key secondary endpoints, change from baseline in pre-BD FEV_1, change from baseline in AQLQ(S)+12 total score, change from baseline in ACQ-6, and change from baseline in weekly mean Asthma Symptom Diary score, the nominal power is 95% or higher (using a nominal 2-sided significance level of 5%), assuming standard deviations of 400 mL and 1.3, 1.3, and 1.3 units respectively, and true differences of 100 mL and 0.3, 0.3, and 0.3 units respectively. The minimum detectable differences, under the above assumptions, are 50 mL for FEV_1, 0.16 for AQLQ(S)+12 total score, and -0.16 for each of Asthma Symptom Diary score and ACQ-6 score.

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 also be used for the reporting of disposition.

2.1.1 Efficacy analysis set

Full analysis set (FAS)

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

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

The FAS specifies which subjects are included in efficacy analyses. Details of which data are included in efficacy analyses for these subjects are given in the respective sections, notably in Section 2.1.5, Section 3.1.4 and Section 4.2.

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

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

2.1.2 Safety analysis set

Safety analysis set

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

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

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

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

2.1.3 Other analysis set

PK analysis set

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

2.1.4 Handling of other issues which may impact analysis sets

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

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

2.1.5 Definition of on-treatment

Efficacy analyses

Any efficacy assessment date which occurs between the date of randomisation and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal) will be considered on-treatment. 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

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

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

2.2 Violations and deviations

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

- Did not fulfil key eligibility criteria
- Developed discontinuation criteria but continued IP
- Received prohibited concomitant medication
- Did not comply with restrictions during the study
- Did not adhere to protocol-required procedure
- IP management issues
- GCP violation deviations
- Safety reporting and other safety deviations

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

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

The study PD 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 and pharmacokinetic variables. If there is no value prior to first dose of study treatment, then the baseline value will not be imputed, and will be set to missing.

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

For weekly mean scores derived from subject eDiary (including, but not limited to, Asthma Symptom Diary 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 date of randomisation and ends with the morning measurement on the day of randomisation.

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

For home-based FENO, 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. For a subject who receives the first dose as scheduled at the randomisation visit, the "most recent week" starts 7 days prior to date of randomisation and ends 1 day prior to date of randomisation.

Baseline for CGI-C and PGI-C is not applicable by definition of these variables.

For safety variables (vital signs, weight/BMI, haematology, clinical chemistry, urinalysis, 12-lead ECG), baseline will be defined as the latest non-missing assessment prior to first dose. If no time is recorded for an assessment, and the assessment takes place at Visit 3, 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 (efficacy) / date of first dose of IP (safety) and ending on the date of the Week 52 visit or earlier study withdrawal date (for subjects not followed up until Week 52).

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

- Post-treatment period/Follow-up period: starting one day after the end date of 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 subjects entering the extension study, the study completion date will be the day of enrolment in the extension study.

- On-study period (planned treatment and follow-up): starting on the date of randomisation (efficacy) / date of first dose of IP (safety) and ending on the study completion or withdrawal date. Note: for subjects entering the extension study, the study completion date will be the day of enrolment in the extension study. For analysis performed at primary database lock, the on-study period is understood to include all data recorded up until the date of the data cut-off for the primary

database lock (which includes all follow-up data available at the time of the data cut-off).

3.1.5 Visit windows

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

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

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

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

- The non-missing value closest to the target day will be selected for analysis at that visit
- If two non-missing values are the same distance from the target day, the earlier of the two values will be selected for analysis at that visit
- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time will be selected for analysis at that visit.

- If two non-missing values (for continuous variables) are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit. For categorical variables in this situation, the worst case will be used.

- If there are multiple ADA samples in the same visit window with both positive and negative results, the sample with a positive result and the highest titer value should be selected.

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

The same visit window definitions below will be used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.1.4). 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, unless it is indicated below that the visit windows in Table 2 or Table 3 should be used.

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

Time Point	Target Day	Visit Window
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	351-378
Follow-up Week 58	407	379-427
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
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

Time Point	Target Day	Visit Window
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, height (adolescents only), SGRQ score, SNOT-22 score, WPAI+CIQ scores and post-BD spirometry.

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.

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

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

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

Essentially the above says that:

- Prior and concomitant medications are mutually exclusive.
- Concomitant medications on-treatment and post-treatment are also mutually exclusive (here, the word “concomitant” means concomitant with study procedures, irrespective of whether IP was still being taken). Specifically, a concomitant

medication which started on-treatment and ended post-treatment will only be considered on-treatment.

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

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

In the above, note that for subjects entering the extension study, the study completion date will be the day of enrolment in the extension study.

3.1.7 Definition of subgroups

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

- *Baseline eosinophils group: <300/μL, ≥300/μL
- *Baseline eosinophils group: <150/μL, 150-<300/μL, 300-<450/μL, ≥450/μL
- *Baseline eosinophils group: <150/μL, ≥150/μL
- *Baseline clinic visit FENO group: <25ppb, ≥25ppb
- *Baseline clinic visit FENO group: <25ppb, 25-<50ppb, ≥50ppb
- Baseline (Any) specific IgE status (FEIA): Any FEIA positive, All FEIA negative, Unknown FEIA
    - "Any FEIA positive" requires 1 or more specific IgE panels using fluorescent enzyme immunoassay (FEIA) to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 12 panels to be available.

- "All FEIA negative" requires all 12 specific IgE panels to be negative. If there are fewer than 12 panels with data available and none of these is positive, then IgE status is considered "Unknown FEIA".
- Positive is defined as a value ≥0.35 kU/L.

- * Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA
  - "Any perennial FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 8 panels to be available.
  - "All perennial FEIA negative" requires all 8 specific IgE panels to be negative. If there are fewer than 8 panels with data available and none of these is positive, then IgE status is considered "Unknown perennial FEIA".
  - Positive is defined as a value ≥0.35 kU/L. The 8 panels include: American Cockroach, Cat Dander, D. farina, D. pteronyssinus, Dog Dander, German Cockroach, Mould Mix, Oriental Cockroach.
- Baseline seasonal specific IgE status (FEIA): Any seasonal FEIA positive, All seasonal FEIA negative, Unknown seasonal FEIA
  - "Any seasonal FEIA positive" requires 1 or more specific IgE (FEIA) panels to be positive. Provided that at least one IgE panel is positive, no further requirement is made for data on all 4 panels to be available.
  - "All seasonal FEIA negative" requires all 4 specific IgE panels to be negative. If there are fewer than 4 panels with data available and none of these is positive, then IgE status is considered "Unknown seasonal FEIA".
  - Positive is defined as a value ≥0.35 kU/L. The 4 panels include: Grass Mix Pollen, Silver Birch Pollen, Weed Mix Pollen, Japanese Cedar.
- *ICS dose at study entry: medium, high (as defined in CSP Appendix F)
- *OCS at baseline: present, absent
  - OCS at baseline will be defined as OCS administered at baseline for disease under study.
- Age category used for stratification: adults (≥18) and adolescents (≥12 to <18)
- *Age category: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18)

- *Gender: Male, Female
- *Race: White, Black or African American, Asian, Other
- *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 protocol deviation in this regard.
- *Baseline body mass index (BMI): <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2*Geographical region: Asia Pacific [incl. Japan, China, South Korea, Taiwan and Vietnam], North America [incl. Canada and USA], South America [incl. Argentina and Brazil], Central/Eastern Europe [incl. Russia and Ukraine], Western Europe plus Australia [incl. Austria, France, Germany, UK and Australia], Rest of World [incl. Israel, Saudi Arabia and South Africa]
- Country
- Baseline CRSwNP status: Yes, No
    - Chronic rhinosinusitis with nasal polyps at baseline 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
    - Nasal polyps at baseline 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 status: Yes, No
    - 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

- Chronic sinusitis at baseline will be defined by the diagnosis of chronic sinusitis on the Respiratory Disease History eCRF page for a particular subject.

- Rhinitis status at study entry: Yes, No
  - Rhinitis at baseline will be defined by the diagnosis of rhinitis on the Respiratory Disease History eCRF page for a particular subject.

- *Biomarker quartiles
  - The four, mutually exclusive, biomarker quartiles will be derived using the baseline FENO, eosinophil and total serum IgE data. This will ensure that the same quartiles will be used for all endpoints analysed.

- #Weight quartiles
  - The four, mutually exclusive, weight quartiles will be derived using the baseline weights.

- #Drug concentration exposure quartiles
  - The four, mutually exclusive, quartiles will be derived using the median trough steady state drug concentration data. The median trough steady state is calculated as the median of the observed drug concentration data at weeks 24, 36 and 52 for each individual 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 from eCRF – date of first dose of IP] + 1.

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

Time to premature study withdrawal

Time to premature study withdrawal will be defined as follows:

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

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

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

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

3.2 Derivation of efficacy variables

3.2.1 Primary endpoint

3.2.1.1 Annualised asthma exacerbation rate over 52 weeks

An asthma exacerbation (recorded on the exacerbation eCRF page) 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 or urgent care visit (defined as evaluation and treatment for <24 hours in an ER or UC centre) due to asthma that required systemic corticosteroids (as per above)
- An inpatient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

The start of an exacerbation is defined in the CSP as the start date of 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 stop date to calculate duration.

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

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

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

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

> *Time at risk (days) = [earliest (Date of Visit 17; date of last exacerbation assessment status from the eCRF) – 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 exacerbation assessment during planned treatment) – date of randomisation] + 1,*

where:

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

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

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

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

For the 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 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 score

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

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

Weekly mean scores and changes from baseline for daytime, night-time, daily scores and individual items will also be calculated. Weekly mean scores for baseline are defined in Section 3.1.1. For the Week 1 mean post-baseline, the week will start with the evening

measurement on the day of randomisation and will end with the morning measurement one week later (i.e. 7 daily pairs, where one day is defined as evening followed by morning). If more than 3 days are missing, then the Week 1 mean will be missing. Weekly mean scores for all subsequent weeks will be defined similarly, with the same rule for handling missing days.

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

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 emergency room 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).

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.

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

3.2.3.2 Other clinic visits 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)
- Limit activities (daytime item).

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:

1. 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.

Subjects without an exacerbation will be censored on the date of last exacerbation assessment, 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, if the planned treatment period 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 (to Week 52) 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 did not complete the planned treatment and had an asthma exacerbation will be defined as not having a successful outcome for this endpoint [d].

	No exacerbation	Exacerbation
Completed planned treatment period	[a] Exacerbation free/successful outcome	[d] No successful outcome
Did not complete 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 hospitalisation or ER visits during the planned treatment period will also be calculated similarly. A subject who only had an exacerbation which did not lead to hospitalisation or ER visit will 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:

- Fractional exhaled nitric oxide (clinic visit FENO; note that this is distinct from home-based FENO in Section 3.2.5.5)
- Peripheral blood eosinophils (10**9/L and Cells/μL)
- Total serum IgE (mg/L and IU/mL)

The definition of baseline is given in Section 3.1.1.

For clinic visit FENO, it is expected that one technically acceptable measurement will be performed at each relevant visit. In the event that more than one technically acceptable FENO measurement is available on the same date at the clinic, all data will be transferred, and the first available technically acceptable FENO measurement on that date will be used. Multiple FENO measurements on different dates will be handled according to the rules for unscheduled/repeat visits (see Section 3.1.5).

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 items assessment each morning and evening, used for the alerts system. This is not the same as the total 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 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 day 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 that required 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. Asthma symptom daytime score (recorded in the evening), night-time score (recorded in the morning) and total score will be calculated and presented separately.

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

For weekly mean scores derived from subject eDiary, baseline is defined in Section 3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 3.2.2.4.

3.2.4.4 Home-based peak expiratory flow

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

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

For weekly means derived from home-based PEF, baseline is defined in Section 3.1.1. The weekly mean calculations and rules for missing days are similar to those for ASD in Section 3.2.2.4.

3.2.4.5 Health resource utilisation

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

Planned treatment period number of days/times and on-study number of days/times will be calculated for each subject for the following variables:

- 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 eCRF page 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 eCRF page up to Week 64.

3.2.4.6 Work productivity and activity impairment

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

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

1. Currently employed (yes/no)

2. Hours missed work due to health problems

3. Hours missed work due to other reasons

4. Hours actually worked

5. Degree health affected productivity while working (0-10 scale, with 0 meaning no effect)

6. Attends class in an academic setting (yes/no)

7. Hours missed class due to health problems

8. Hours actually attended class

9. Degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)

10. Degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

If the answer to question 1 is 'No, not currently employed', then the subject should skip to question 6. If the answer to question 6 is 'No, not currently attending class', then the subject should skip to question 10.

The WPAI+CIQ provide 4 scores:

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

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

For each time point at which the WPAI-CIQ is administered, the following descriptive

statistics (if applicable) (n, total number of hours, mean per subject, standard deviation (SD), median, minimum and maximum) will be reported for those who are employed:

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

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

- # currently employed – Yes in response to Question 1
- # of hours missed due to asthma – as responded in Question 2
- Absenteeism = Q2/(Q2+Q4)
- Presenteeism = Q5/10
- Work Productivity Loss = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
- Activity Impairment = Q10/10

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

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

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

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

In addition, activity impairment will be presented for those who are not employed, not in school, and all subjects.

3.2.4.7 EQ-5D-5L score

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

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

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

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

3.2.4.8 Patient and clinician global impression scores

The Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) instruments are used to evaluate the overall response to treatment. For the CGI-C the investigator (clinician) will be asked to rate the degree to which the overall asthma status may have changed when compared to baseline. The assessment uses a 7-point rating scale: 1 = Very Much Improved; 2 = Much Improved; 3 = Minimally Improved; 4 = No Change; 5 = Minimally Worse; 6 = Much Worse; 7 = Very Much Worse. The PGI-C asks subjects to report change from baseline using the same scale as the CGI-C.

The Patient Global Impression of Severity (PGI-S) is a single item designed to capture the subject's perception of overall symptom severity at the time of completion using a 6-point categorical response scale (0 = No Symptoms; 1 = Very Mild Symptoms; 2 = Mild Symptoms; 3 = Moderate Symptoms; 4 = Severe Symptoms; 5 = Very Severe Symptoms).

For CGI-C and PGI-C subjects will also be categorized as Improved, Much Improved and Very Much Improved according to the following responses post-baseline:

- Improved: subjects in this category will include those with responses of 'very much improved', 'much improved 'and 'minimally improved'.
- Much Improved: subjects in this category will include those with responses of 'very much improved' and 'much improved'.
- Very Much Improved: subjects in this category will include those with responses of 'very much improved'.

Subjects can be counted in more than one category at a given time point.

Calculation of percentages will be based on the number of subjects in the FAS with a completed assessment. There will be no imputation for missing values.

3.2.5 Exploratory endpoints

CCI

CCI

[redacted]

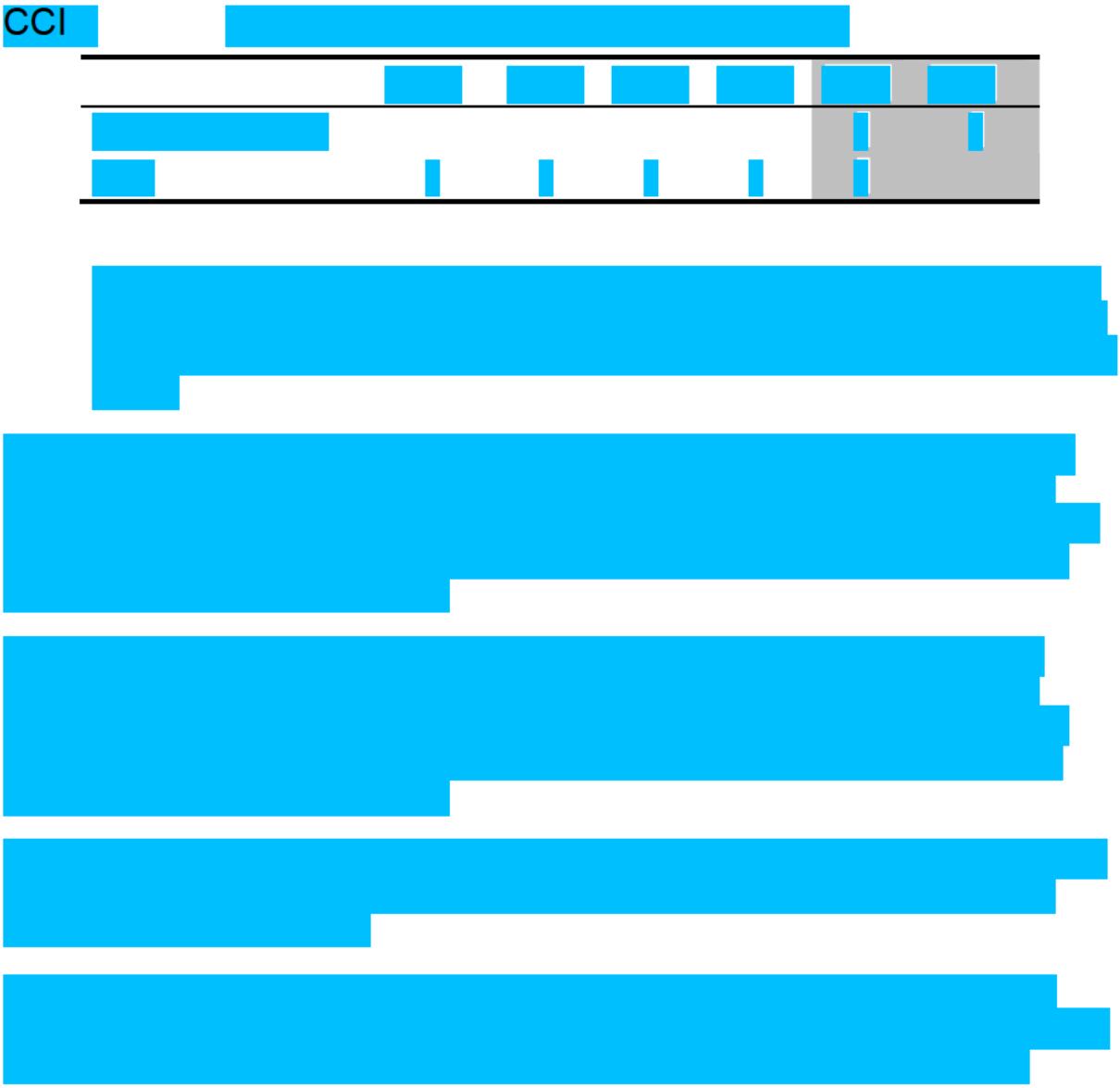
s

CCI

CCI

[redacted]

CCI



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 – general

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

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

- 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 period (for subjects still being followed up then): date of last dose of IP + 33 days < AE onset date ≤ study completion or withdrawal date
- AEs occurring during on-study period: date of first dose of IP ≤ AE onset date ≤ study completion or withdrawal date.

In the above, note that for subjects entering the extension study, the study completion date will be the day of enrolment in the extension study.

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

If the AE has a partially missing (and unresolvable) onset date, then the AE will also be assumed to have occurred during the on-treatment period, unless either the end date indicates

unambiguously that the AE resolved before treatment started, or the partial onset date is in the month/year prior to start of treatment.

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

Study adjusted incidence rates will be defined as the number of subjects reporting adverse events divided by duration of the on-study period for each subject as defined in Section 3.1.2.

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

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

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

3.3.3 Adverse events of special interest

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

3.3.4 Laboratory variables

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

Changes from baseline in continuous laboratory variables will be calculated at relevant visits as specified in 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 display of liver function tests.

3.3.5 Vital signs

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

BMI is calculated as:

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

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

Table 6 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change from Baseline Criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (sitting)	mmHg	90	160	±30
Pulse rate (sitting)	beats/min	50	100	±20

Parameter	Standard Units	Lower Limit	Upper Limit	Change from Baseline Criteria
Respiratory rate	breaths/min	8	20	
Body temperature	Celsius	36.0	37.5	
Weight	kg	40	150	

3.3.6 12-lead digital ECG

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

Changes from baseline in continuous 12-lead 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 and immunogenicity variables

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

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

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

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

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

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Statistical hypotheses for confirmatory endpoints

The following two-sided hypotheses will be evaluated in this trial. The nominal significance levels and methodology for accounting for multiplicity in testing these hypotheses is described in Section 4.1.2.

Primary endpoint – all subjects

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.

AAER – subjects with baseline eosinophils < 300/µL

H02: AAER ratio over 52 weeks (tezepelumab/placebo) = 1

versus

H12: 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 – all subjects

H03: Difference in mean change from baseline in pre-BD FEV_1 at 52 weeks (tezepelumab minus placebo) = 0

versus

H13: 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.

H04a: Difference in mean change from baseline in AQLQ(S)+12 total score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14a: 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.

H04b: Difference in mean change from baseline in ACQ-6 score at 52 weeks (tezepelumab minus placebo) = 0

versus

H14b: 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.

H05: Difference in mean change from baseline in weekly mean Asthma Symptom Diary score at 52 weeks (tezepelumab minus placebo) = 0

versus

H15: Difference in mean change from baseline in weekly mean Asthma Symptom Diary 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 primary endpoint (in all subjects) will be tested at the 0.01 level to further ensure statistically persuasive evidence. If the primary analysis of AAER in all subjects observes $p \leq 0.01$, the trial will be declared successful. In order to assess the primary objective of effect across the all-comer population, the subgroup of subjects with baseline eosinophils < 300/µL has been added into the multiple testing procedure following direction from the FDA.

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 1% significance level regarding the primary endpoint (AAER) in all subjects.

Level 2

If H01 is rejected at the 2-sided 1% significance level, then the null hypothesis H02 will be tested at a 2-sided 5% significance level regarding the AAER in subjects with baseline eosinophils < 300/µL.

Level 3

If H02 is rejected at the 2-sided 5% significance level, then the null hypothesis H03 will be tested at a 2-sided 5% significance level regarding change from baseline in pre-BD FEV_1.

Level 4

If H03 is rejected at the 2-sided 5% significance level, then the null hypotheses H04a and H04b 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 4 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 4 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 ($0 \leq \gamma \leq 1$).

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 4 in order to claim significance, versus the ability to subsequently claim significance from formal hypothesis testing in Level 5. In this trial γ will be set to 0.5.

Using this choice of truncation parameter, the higher of the two Level 4 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 H04a and H04b will be rejected, and testing will proceed to Level 5. If it is not significant at the 3.75% level, then the lower of the 2 Level 4 p-values will be evaluated at a 2.5% significance level (2-sided). If it is significant, then the relevant null hypothesis (either H04a or H04b) will be rejected, and testing will proceed to Level 5. If it is (also) not significant, then formal testing will stop at Level 4. The significance levels for subsequent evaluation in Level 5 for each of these scenarios are given below.

Level 5

The null hypothesis H05 will be tested at the significance level retained from Level 4, which depends on the outcomes in Level 4 as follows:

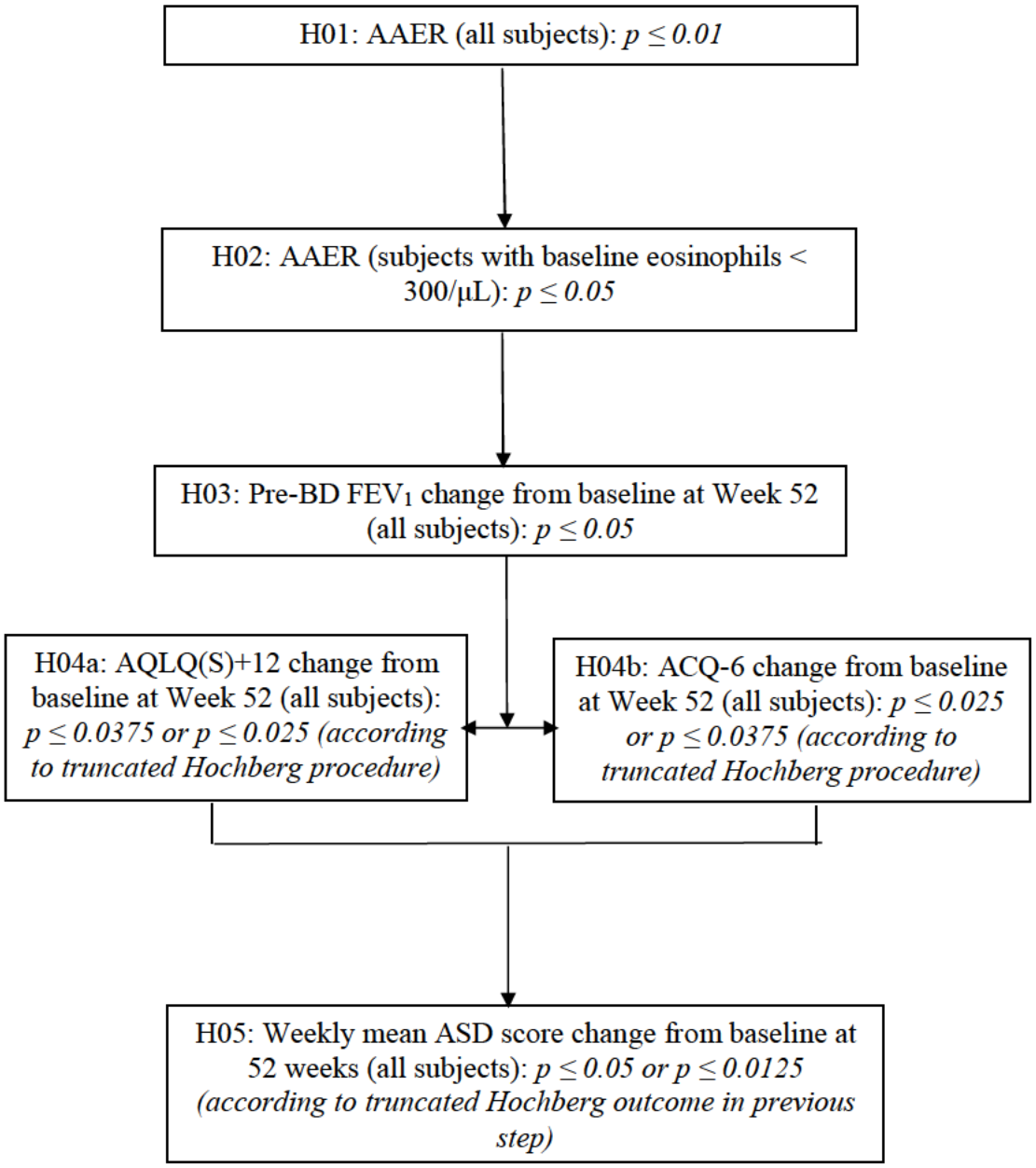
- Case 1: If both comparisons in Level 4 exhibit statistical significance, then H05 will be tested at a 2-sided 5% significance level with regard to change from baseline in weekly mean ASD score.

- Case 2: If only one of the comparisons in Level 4 exhibits statistical significance, then H05 will be tested at the 2-sided significance level $\alpha - [\gamma\alpha + (1-\gamma)\alpha/2]$ retained from Level 4, where $\alpha = 0.05$.

Using the proposed choice of $\gamma = 0.5$, if both H04a and H04b were rejected in Level 4, then H05 in Level 5 will be tested at a 2-sided 5% significance level (Case 1). If only one of H04a and H04b was rejected in Level 4, then H05 in Level 5 will be tested at a 2-sided 1.25% significance level (Case 2).

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

Figure 1 Multiple testing procedure



4.2 Analysis methods

4.2.1 Subject disposition, demography and baseline characteristics

Subject disposition will be summarised using the all subjects analysis set. The number of enrolled subjects will be summarised. The number and percentage of subjects within each treatment group will be presented by the following categories; randomised, not randomised

(and reason), received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and discontinued study (including reason). Subject recruitment by country and centre will also be summarised.

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

Disposition will also be provided for the number and percentage of randomised subjects who consented separately to participate in the optional sub-studies (DNA sampling, flow cytometry, home-based FENO).

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

Disposition summaries will also be produced for the age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18).

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 factors 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 by treatment group for the FAS.

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

Baseline biomarker variables (FENO, eosinophils and IgE) will also be summarised by treatment for the FAS.

Demographic data, various baseline characteristics and baseline biomarker variables will also be summarised by treatment and the following categorical variables for the FAS:

- Baseline eosinophils group: <300/µL, ≥300/µL
- Age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18).

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 codes and generic name) will be presented by treatment for the FAS. Separate tables will be presented for all medications received during each of the following periods as defined in Section 3.1.6: Prior, Concomitant (on-treatment), Concomitant (post-treatment).

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose categories (low/medium/high) of ICS medications. The number of subjects using other maintenance asthma medications at baseline will also be summarised. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per patient from the first day of IP up to Week 52 will also be summarised.

The number of subjects using other maintenance asthma medications at baseline will also be summarised for the age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18).

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

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

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

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

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

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

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

4.2.3 Exposure and compliance

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

Extent of exposure to IP, compliance, and total number of dosing occasions will be summarised by treatment group, for the safety analysis set. These data will also be summarised for the age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18).

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. These data will also be summarised for the age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18).

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 uses a treatment policy strategy and will therefore include all available data after treatment discontinuation until the end of the planned treatment period.

Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 52-week period even after premature discontinuation of IP. Consequently, subjects lost to follow-up, subjects who die and subjects who withdraw their consent should be the only source of missing information for the primary analysis.

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

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model. This model will be used to perform the statistical test of the null hypothesis specified in Section 4.1.1 and to estimate the treatment effect and both its 99% and 95% confidence intervals.

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, age (adolescents or adults) and history of exacerbations (<=2 or >2 in previous 12 months) will be included as factors in this model. 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 divided by the total time at risk for that treatment).

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

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 both MAR and missing not at random (MNAR)/dropout reason-based (DRMI) assumptions respectively:

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

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

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

   Table 7 summarises how tezepelumab subjects withdrawing from study will be handled in the DRMI analyses described above. The rules in the table will be applied irrespective of the length of time between discontinuing IP and withdrawing from study (noting that the treatment policy strategy is used for these sensitivity analyses).

Table 7 Treatment arms for imputation of tezepelumab subjects under DRMI

Reason for withdrawing from study	Reason for discontinuing IP	DRMI
Death		Placebo
Site terminated by sponsor		Tezepelumab
Study terminated by sponsor		Tezepelumab
Loss to follow-up Withdrawal by Subject Withdrawal by parent/guardian Other	Death	Placebo
	Adverse event	Placebo
	Development of study-specific discontinuation criteria	Placebo
	Severe non-compliance to protocol	Placebo
	Subject lost to follow-up	Placebo by default (pending blinded review of any further information)
	Subject decision	Placebo by default (pending blinded review of any further information)
	Other	Placebo by default (pending blinded review of any further information)

A blinded review of subjects who 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 reason for study withdrawal was not related to treatment, then the "Placebo" default for DRMI in the above table may be changed for that subject.

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

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

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

Step 2: Drawing samples from the posterior distribution

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

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

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

A random seed of 991511 will be used. The first 2000 iterations will be discarded to allow for convergence to a stationary distribution and to remove the effect of the starting values ("burn-in"). A gap of 100 iterations will be used between imputations to ensure independence between imputations ("thinning").

Step 3: Imputing missing data

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

- $k^* = k + Y_1$
- $p^* = (k + \varphi_1) / (k + \varphi_1 + \varphi_2)$
- φ_1 is the expected number of events prior to withdrawal
- φ_2 is the expected number of events after withdrawal

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

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

Step 4: Multiple imputation algorithm

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

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

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

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

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

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

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

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

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

Tipping point analysis

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

In this analysis, various degrees of improvement in the placebo group $p_{p.}$ after withdrawal, and various degrees of worsening in the tezepelumab group δ_T after withdrawal, will be simultaneously explored.

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

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

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

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

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

This corresponds to values of δ_P between 0.22 and 1, and values of δ_T between 1 and 4.5. If a tipping point was observed with analysis using 0.5 increments, smaller increments e.g. of 0.25 may need to be explored in the relevant range to determine the tipping point more precisely.

4.2.4.3 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 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.

Annualised rate 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.

These supporting analyses will be performed using the treatment policy strategy 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 subgroups 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/µL, ≥300/µL
- Baseline eosinophils group: <150/µL, 150-<300/µL, 300-<450/µL, ≥450/µL
- Baseline eosinophils group: <150/µL, ≥150/µL
- Baseline clinic visit FENO group: <25ppb, ≥25ppb
- Baseline clinic visit FENO group: <25ppb, 25-<50ppb, ≥50ppb
- Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA

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. This includes the analysis of AAER in subjects with baseline eosinophils < 300/µL which is specified in Section 4.1.2.

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)).

The categorical subgroup analysis above will also be repeated using the four (mutually exclusive) categories defined by the quartiles of each baseline biomarker.

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: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18)
- Gender: Male, Female
- Race: White, Black or African American, Asian, Other
- Exacerbations in the year before study: ≤2 exacerbations, >2 exacerbations
- OCS at baseline: present, absent
- Baseline body mass index (BMI): <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2
- Geographical region: Asia Pacific, North America, South America, Central/Eastern Europe, Western Europe plus Australia, Rest of World
- Nasal polyps in the 2 years before randomisation: Yes, No

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.

For age, the above categorisation will replace the one used in the primary analysis model.

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 separately for:

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

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-bronchodilator FEV_1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean 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 for subjects who discontinued study treatment prior to Week 52.

This analysis uses a treatment policy strategy and will therefore include all available data after treatment discontinuation until the end of the planned treatment period.

Subjects will be encouraged to continue to undergo applicable study related visits/procedures for the full 52-week period even after premature discontinuation of IP. Consequently, subjects lost to follow-up, subjects who die, subjects who withdraw their consent and subjects who choose Option 3 for their follow-up should be the only source of missing information for the key secondary analyses apart from subjects who choose Option 2 for their follow-up, who will have missing pre-BD FEV_1 following discontinuing of IP until their Week 52 visit.

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 mixed model for repeated measures (MMRM) model. 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% confidence interval, for each endpoint.

The response variable in the model will be change from baseline at each scheduled post-randomisation visit up to and including Week 52, and irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region, age (adolescents or adults) 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 the MMRM model.

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

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

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

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

4.2.5.2 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. 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.

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

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

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

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

Step(a):

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.

Step(b):

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.

<u>MNAR/DRMI</u>

To impute missing values at time *t* for subjects in the tezepelumab arm 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.

To impute missing values at time *t* for all placebo subjects and tezepelumab subjects who withdrew from the 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* from 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 MMRM model specified in Section 4.2.5.1. 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).

Tipping point analysis

A tipping point analysis will be performed for each of the four continuous key secondary endpoints, using similar multiple imputation methodology. In this analysis, various degrees of improvement in the placebo group δ_P after withdrawal, and various degrees of worsening in the tezepelumab group δ_T after withdrawal, will be simultaneously explored.

Placebo subjects who withdrew from the study (irrespective of reason for discontinuing IP) will have their first imputed value improved by δ_P. This results in a one-time shift towards a better value in the outcomes of placebo subjects that withdrew from the study after a given visit. Tezepelumab subjects who withdrew from the study (irrespective of reason for discontinuing IP) will have their first imputed value worsened by δ_T. This results in a one-time shift towards a worse value in the outcomes of tezepelumab subjects that withdrew from the study after a given visit.

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

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

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

For pre-BD FEV_1 change from baseline:

- δ_P will be varied from 0 to 0.3 L in increments of 0.1 L
- δ_T will be varied from 0 to -0.3 L in increments of 0.1 L.

If a tipping point was observed with analysis using 0.1 mL increments, smaller increments of 0.05 mL will then be explored in the relevant range to determine the tipping point more precisely.

For AQLQ(S)+12 total score change from baseline:

- δ_P will be varied from 0 to 3 in increments of 1
- δ_T will be varied from 0 to -3 in increments of 1.

If a tipping point was observed with analysis using increments of 1, smaller increments of 0.5 will then be explored in the relevant range to determine the tipping point more precisely.

For ACQ-6 score change from baseline:

- δ_P will be varied from 0 to -3 in increments of 1
- δ_T will be varied from 0 to 3 in increments of 1.

If a tipping point was observed with analysis using increments of 1, smaller increments of 0.5 will then be explored in the relevant range to determine the tipping point more precisely.

For weekly mean daily ASD score change from baseline:

- δ_P will be varied from 0 to -2 in increments of 1
- δ_T will be varied from 0 to 2 in increments of 1.

If a tipping point was observed with analysis using increments of 1, smaller increments of e.g. 0.5 may need to be explored in the relevant range to determine the tipping point more precisely.

4.2.5.3 Supplementary analyses

The MAR 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.

4.2.5.4 Supporting analyses

As a supportive analysis to the analysis of change from baseline in ACQ-6, the main ACQ-6 analysis described in Section 4.2.5.1 will be repeated for change from baseline in ACQ-5 and ACQ-7 score using a similar MMRM model. Similar descriptive and graphical summaries will also be produced.

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 MMRM model.

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 MMRM model.

As further supportive analyses to the analyses of change from baseline in ACQ-6, AQLQ(S)+12 and weekly mean ASD, responders/non-responders will be summarised descriptively and analysed using a generalised linear model for repeated measures, using a logit link function. The response variable in the model will be the binary responder status at each scheduled post-randomisation visit up to and including Week 52, irrespective of whether the subject remained on treatment and/or took other treatments. Treatment, visit, region, age (adolescents or adults) 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.

In this model, inference will be based on generalised estimating equations (GEEs) using the method of Liang and Zeger (1986). An unstructured working correlation matrix will be used, along with empirically corrected standard errors. 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 on-study period for each post-baseline week using descriptive statistics.

As further supportive analysis to the analysis of change from baseline in weekly mean total (daily) ASD score, the main ASD analysis 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 MMRM model. Similar descriptive summaries will also be produced.

As further supportive analysis to the analysis of change from baseline in weekly mean total (daily) ASD score, the main ASD analysis 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 MMRM model. Similar descriptive summaries will also be produced.

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-bronchodilator FEV_1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean 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/μL, ≥300/μL
- Baseline eosinophils group: <150/μL, 150-<300/μL, 300-<450/μL, ≥450/μL
- Baseline eosinophils group: <150/μL, ≥150/μL
- Baseline clinic visit FENO group: <25ppb, ≥25ppb
- Baseline clinic visit FENO group: <25ppb, 25-<50ppb, ≥50ppb
- Baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA

A similar MMRM model 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.

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 and used to evaluate time of onset of effect within each biomarker subgroup category (baseline eosinophils <300/μL, ≥300/μL; baseline clinic visit

FENO group: <25ppb, ≥25ppb; baseline perennial specific IgE status (FEIA): Any perennial FEIA positive, All perennial FEIA negative, Unknown perennial FEIA).

Standardised effect plots will be produced for each of the key secondary endpoints, similar to what was described in Section 4.2.4.5.

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.

The categorical subgroup analysis above will also be repeated, for each of the key secondary endpoints, using the four (mutually exclusive) categories defined by the quartiles of each baseline biomarker.

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: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18)
- Gender: Male, Female
- Race: White, Black or African American, Asian, Other
- Exacerbations in the year before study: ≤2 exacerbations, >2 exacerbations
- OCS at baseline: present, absent
- Baseline body mass index (BMI): <18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, ≥30.0 kg/m^2
- Geographical region: Asia Pacific, North America, South America, Central/Eastern Europe, Western Europe plus Australia, Rest of World
- Nasal polyps in the 2 years before randomisation status: Yes, No

A similar MMRM model 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.

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

For age, the above categorisation will replace the one used in the main analysis models for the key secondary endpoints.

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.

Standardised effect plots will be produced separately for:

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

4.2.6 Other secondary endpoints

Annualised rates for supporting exacerbation endpoints will be summarised and analysed as described in Section 4.2.4.3.

Other binary endpoints will be summarised descriptively and analysed using a logistic regression model with factors which will include treatment, region and age (adolescents or adults). 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/µL, ≥300/µL

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 an MMRM 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 continuous other secondary endpoints:

- Change from baseline in pre-BD $FEF_{25-75\%}$ analysed using MMRM and summarised descriptively; other pre-BD clinic visit spirometry only summarised descriptively.
- Change from baseline in biomarkers (clinic visit FENO, eosinophils (10**9/L and Cells/µL) and total serum IgE (mg/L and IU/mL)) analysed using MMRM and summarised descriptively. These summaries and analyses will be repeated for the age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18). 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 total daily asthma symptom score analysed using MMRM and summarised descriptively; weekly mean daytime and night-time asthma symptom scores only summarised descriptively.
- Change from baseline in weekly mean daily rescue medication use, night-time awakenings, morning home-based PEF and evening home-based PEF analysed using MMRM; any other eDiary variables only summarised descriptively.
- All HRU items defined in Section 3.2.4.5 only summarised descriptively.
- All WPAI+CIQ scores defined in Section 3.2.4.6 only summarised descriptively.
- Change from baseline in EQ-5D-5L VAS and health state valuation index analysed using MMRM; other EQ-5D-5L dimensions only summarised descriptively.
- CGI-C, PGI-C and PGI-S only summarised descriptively.

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, age (adolescents or adults), 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 (only) will be analysed similarly to time to first asthma exacerbation for any reason above.

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 and ≥300/μL only).

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

CCI

- CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

4.2.8 Safety and tolerability

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

4.2.8.1 Adverse events

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 will be listed, but not summarised separately.

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

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

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

- SAEs
- Fatal AEs
- DAEs
- DAEs causally related to IP
- SAEs leading to discontinuation of IP

- Each AESI category separately
- The most common AEs (defined as those occurring in >3% of subjects in either treatment group) – by PT only

All AEs (by PT) will be summarised additionally by causality and maximum intensity. If a subject reports multiple occurrences within each SOC and 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.

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

- Site of injection (arm, thigh, abdominal wall)
- Total number of doses administered (1, 2, …, 13), irrespective of timing of the injection site reaction event.

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

- All AEs
- Each AESI separately

In these summaries, the exposure-adjusted rate will be defined for each treatment as the number of subjects in that treatment group reporting the AE divided by the total time at risk for all subjects in that treatment group, the latter as defined in Section 3.3.2. Rates will be reported as events per 100 subject-years.

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

The following AE summaries will be produced by treatment group and age category (adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18)):

- Overall summary table as described above, for the on-treatment and on-study periods.
- The most common AEs (defined as those occurring in >3% of subjects in either treatment group), by PT, for the on-treatment and on-study periods.
- AEs summarised by SOC and PT, for the on-treatment and on-study periods.
- SAEs summarised by SOC and PT, for the on-treatment and on-study periods.
- AEs summarised by PT and maximum intensity.

- DAEs summarised by SOC and PT.

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/last post-baseline values for each variable.

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

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

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/last value post-baseline. All data for the on-study period will be used.

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

4.2.8.3 Vital signs

All vital signs variables will be summarised by absolute value at each visit by treatment group, together with the corresponding changes from baseline. This will also include weight, BMI and height (for adolescents only). 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/last post-baseline values for each variable.

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

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

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

4.2.8.4 12-lead digital ECG

Continuous 12-lead 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 Fredericia corrected QT (QTc) values and increases from baseline at any time during the on-study period using standard pre-specified thresholds will be produced.

4.2.8.5 Physical examination

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

4.2.9 Pharmacokinetics and immunogenicity

4.2.9.1 Analysis of pharmacokinetics

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

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

Serum samples for PK are scheduled to be collected at weeks 0, 4, 12, 24, 36, 52, 64 and at the premature IP discontinuation visit, where appropriate. Data will be assigned to weeks based on the windows defined in Section 3.1.5.

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

- Only pre-dose samples at week 0.
- Only pre-dose samples at weeks 4, 12, 24 and 36 that were also between ≥ 21 and ≤ 35 days post the previous dose.
- Only samples that were taken between ≥ 21 and ≤ 35 days post the previous dose for week 52.
- All samples for 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), and separately for adults and adolescents.

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

4.2.9.2 Analysis of immunogenicity

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

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

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

- Subjects who are ADA positive at any time including baseline (ADA prevalence).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and positive in at least one post baseline measurement.
- Subjects who are ADA positive at baseline regardless of post-baseline result.
- Subjects who are ADA positive post-baseline.
- Subjects who are ADA positive post-baseline and ADA negative at baseline (treatment induced ADA)
- Subjects who are persistently positive; persistently positive is defined as having at least 2 post-baseline ADA positive measurements (with ≥ 16 weeks between first and last positive) or an ADA positive result at the last available post-baseline assessment.
- Subjects who are transiently positive; transiently positive is defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive.
- Subjects with treatment boosted ADA, defined as baseline positive ADA titre that was boosted to a 4 fold or higher level following IP administration
- Subjects with treatment emergent ADA (ADA incidence): defined as the sum of treatment induced ADA and treatment boosted ADA.

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

The ADA status across the study will also by summarised for the age subgroups at study entry: adults (≥65), adults (≥18 to <65) and adolescents (≥12 to <18).

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

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

If appropriate, the association of ADA status across the study with primary and key secondary efficacy, biomarkers and AEs/SAEs may be evaluated.

4.2.9.3 Exposure-response analyses

The subgroup analyses described below will be produced to characterise the exposure-response relationship.

- Weight quartiles

  A similar negative binomial model will be fitted as for the primary analysis 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 summarised graphically using a forest plot. The overall treatment effect will be displayed on the forest plot:

  A similar MMRM model will be fitted as for the key secondary endpoint pre-BD FEV_1 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 summarised graphically using a forest plot. The overall treatment effect at Week 52 will be displayed on the forest plot. Adjusted means from this model will additionally be summarised graphically over time.

- Drug concentration exposure quartiles

  Tezepelumab subjects will be grouped according to drug concentration quartiles. The treatment groups referred to in the following analyses will be the drug concentration quartiles and placebo. Each drug concentration quartile will be compared against the overall placebo group.

A similar negative binomial model will be fitted as for the primary analysis. This model will be used to estimate the treatment effect and its 95% CI for each drug concentration quartile, which will be tabulated and summarised graphically using a forest plot. The treatment effect for each drug concentration quartile will be displayed on the forest plot:

A similar MMRM model will be fitted as for the key secondary endpoint pre-BD FEV_1. This model will be used to estimate the treatment effect and its 95% CI for each drug concentration quartile at Week 52, which will be tabulated and summarised graphically using a forest plot. The treatment effect for each drug concentration quartile at Week 52 will be displayed on the forest plot. Adjusted means from this model will additionally be summarised graphically over time.

5. INTERIM ANALYSES

No interim analyses are planned in this trial.

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

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

6. CHANGES OF ANALYSIS FROM PROTOCOL

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

The protocol specifies that one of the exploratory objectives is to explore the effect of 210 mg tezepelumab SC Q4W on total immunoglobulin levels. Total serum IgE is included in Section 1.1.3, Other Secondary Objectives: To assess the effect of 210 mg tezepelumab SC Q4W on biomarkers, so removed from Section 1.1.5.

The protocol defines an emergency room or urgent care visit due to asthma that requires systemic corticosteroids, as one of 3 criteria for a protocol defined exacerbation. However, only information on emergency room visits and use of systemic corticosteroids are collected

in the eCRF. The text in Section 1.1.3, Section 3.2.3.1, Section 3.2.3.3, Section 3.2.4.1, Section 4.2.4.4 and Section 4.2.6 has been updated to reflect this.

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.

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. The daytime and night-time scores from this assessment have also been included.

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

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8. APPENDIX

8.1 Adverse events of special interest

8.1.1 Anaphylactic reactions

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

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

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.

8.1.2 Immune complex disease (Type III hypersensitivity reactions)

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

8.1.3 Malignancy

Malignancy will be defined on the basis of an SMQ.

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.

8.1.4 Helminth infections

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

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

8.1.5 Severe infections (as defined in the protocol)

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

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

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

8.1.6 Injection site reactions

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

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

8.1.7 Opportunistic infections

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

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.

8.1.8 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be

finalised by the study team prior to the primary database lock and provided together with the study datasets at the time of submission.

8.2 OCS conversion factors for prednisone equivalents

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

Table 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[a]

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®)	n.a.	200
Fluticasone propionate	500	>500
Fluticasone propionate HFA	440-500	>500
Budesonide	800	>800
Mometasone furoate	440	>440
Inhaled Corticosteroid in ICS/LABA combination[b]	**Medium**	**High**
Beclomethasone dipropionate (e.g. Fostair®)	400	>400
Fluticasone propionate HFA (e.g. Seretide®, Advair®)	500	>500
Fluticasone furoate (e.g. Relvar® Ellipta®, Breo® Ellipta®)	n.a.	184-200
Budesonide, if as delivered dose (e.g. Symbicort®)	640	>640
Mometasone Furoate (e.g. Dulera®)	400	>400

[a] The Japanese asthma paediatric guidelines will be followed for the Japanese adolescent subject (the medium to high dose for Japanese adolescent subjects 15 years or younger will be ≥ 200 µg/day of FP or other ICSs of equivalent dose).
[b] 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 Additional reporting to assess the impact of the COVID-19 pandemic

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

Section 2.2 Violations and Deviations

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

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

Section 4.2.1 Subject disposition, demography and baseline characteristics

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

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

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

Section 4.2.3 Exposure and Compliance

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

Section 4.2.4.1 Primary analysis (Annualized asthma exacerbation rate)

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

The time at risk for this analysis 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 exacerbation assessment status from the eCRF; 10th March 2020) – 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 exacerbation assessment during planned treatment; 10th March 2020) – date of randomisation] + 1,*

where:

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

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

The number of days the subject experiences a protocol defined exacerbation, including the subsequent 7 days (when a further exacerbation would not be considered as a second exacerbation), will be subtracted from the time at risk defined above for the analysis.

AAER in the tezepelumab group will be compared to that seen in the placebo group using a negative binomial model as described in Section 4.2.4.1. Results will also be included in the forest plot for the primary. Descriptive statistics will also be presented.

Subgroup analyses

The above analysis will also be repeated for the eosinophil subgroup (<300/µL, ≥300/µL), as described in Section 4.2.4.5 based on a hypothetical scenario where only data prior to 11th March 2020 will be included in the analyses.

Section 4.2.5.1 (Key secondary endpoints) Main analysis

Additional analyses of the key secondary endpoints (changes from baseline to Week 52 for each of pre-bronchodilator FEV1, AQLQ(S)+12 total score, ACQ-6 score and weekly mean ASD score) will be performed based on the hypothetical scenario that the COVID-19 pandemic did not occur. A hypothetical strategy will be used which will include all available data during the planned treatment period prior to 11th March 2020. Any data available on or after 11th March 2020 will be set to missing in these analyses.

Change from baseline for the key secondary endpoints in the tezepelumab group will be compared to that seen in the placebo group using a mixed model for repeated measures (MMRM) model as described in Section 4.2.5.1.

The response variable in the model will be change from baseline at each scheduled post-randomisation visit. The same covariance structure will be used for the additional analyses as the key secondary analysis, unless there are convergence issues and selection of the covariance structure will follow the same hierarchical approach as discussed in Section 4.2.5.1.

Adjusted means from the MMRM model above will be displayed graphically over time and included in the same figure as the main analyses results.

Subgroup analyses

The above analysis will also be repeated for the eosinophil subgroup (<300/µL, ≥300/µL), as described in Section 4.2.5.5 based on a hypothetical scenario where only data prior to 11th March 2020 will be included in the analyses.

Section 4.2.8.1 Adverse Events

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

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

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

For the adjudication AE summary tables, the number of subjects reported AEs that were adjudicated to be related to COVID-19 will be included. The adjudication listing will show the

adjudicated relationship to COVID-19 (related, not related, undetermined, and not applicable). Not applicable will be used for AEs with an onset date prior to 01 January 2020.

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