Statistical Analysis Plan	
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A Phase I, Open Label Study to Evaluate the Pharmacokinetics of Tezepelumab in Children ≥ 5 to 11 Years of Age with Mild, Moderate, or Severe Asthma

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
%AUCex	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
$AUC_{0\text{-}inf}$	Area under serum concentration-time curve from time zero (predose) extrapolated to infinity
$AUC_{0\text{-}last}$	Area under the concentration-time curve from time zero (predose) to the last measurable concentration
$AUMC_{0\text{-}inf}$	Area under the moment curve of the analyte in the sampled matrix from zero (predose) extrapolated to infinite time
AZ	AstraZeneca
BLQ	Below the LLOQ
CL/F	Apparent clearance
C_{max}	Maximum observed serum concentration
CSP	Clinical study protocol
CSR	Clinical Study Report
CV%	Coefficient of variation
DBL	Database lock
ECG	Electrocardiogram
EOS	End of Study
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GCV% or GeoCV%	Geometric coefficient of variation
IP	Investigational product
LLOQ	Lower limit of quantification
λ_z	Elimination rate constant
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum

Abbreviation or special term	Explanation
MRD	Minimum required dilution
MRT	Mean residence time
nAb	Neutralising antibodies
ND	Not Determined
CCI	[redacted]
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
CCI	[redacted]
PT	Preferred term
Rsq	Goodness of fit statistic for calculation of λ_z
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SI	Standard international
SOC	System organ class
$t_{1/2}$	Terminal phase elimination half-life
TBL	Total bilirubin
TE-ADA	Treatment-emergent anti-drug antibodies
t_{max}	Time to achieve maximum observed serum concentration
ULN	upper limit of the normal
V_{ss}/F	Apparent steady-state volume of distribution
V_z/F	Apparent volume of distribution

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	01-Aug-22	Section 6: Text has been updated to include Day 29 PK analysis for dose confirmation for safety and efficacy study in 5 to <12 years old children.	No	Day 29 PK analysis after all subjects complete Visit 7 was introduced in order to provide faster confirmation for dose of IP for future safety and efficacy study in 5 to <12 years old children.
Other	01-Aug-22	Section 5: Updated text to "No formal interim analyses are planned in this trial".	Yes	Text added to clarify no formal interim analyses to be conducted.
Other	01-Aug-22	Study details: CSP version updated.	Yes	CSP version was updated to align with the latest one.
Other	01-Aug-22	Section 4.2.2: Removed OCS details and added details of ICS dose conversion factors.	Yes	OCS details removed to be consistent with Exclusion Criterium #6, reference of ICS conversion dose factors added to keep track of version used.
Other	01-Aug-22	Section 4.2.6.1: Removed text "A summary of the most common AEs will be presented by PT.".	N/A	Due to little sample size, the marginal percentage of most common AEs as required per template would be unreasonably high.
Other	01-Aug-22	Section 4.2.6.2: Removed text "For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for each quantitative variable and will include subjects with	N/A	Urinalysis data is no longer collected in terms of quantitative variables for which this text was included. Respective shift table for negative/positive values remains included in the text of this SAP.

		both baseline and post-baseline data."		
Data presentations	01-Aug-22	Section 4.2.6.2: Removed TBL presentations as multiples of ULN ≤1.5, >1.5-2, >2 and AST/ALT as multiples of ULN ≤1, >1-3, >3-5, >5-10, >10.	N/A	These ranges for ULN are not used in any outputs, actually used ranges remain a part of this SAP.
Data presentations	01-Aug-22	Sections 4.2.6.2 and 4.2.6.3: Missing values category and baseline to last post-baseline value shift table removed for clinical laboratory and vital signs.	N/A	Shift tables for baseline to minimum/maximum post-baseline value are sufficient for this study. Missing values category does not provide valuable information in shift table.
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data presentations	01-Aug-22	Section 4.2.1.2: Removed virology results at screening (HBsAg, HCAb, HIV-1, and HIV-2 antibodies) from baseline characteristics summary.	N/A	This data is no longer presented due to privacy reasons.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5180C00025. The SAP describes the statistical analyses specified in version 4.0 of the clinical study protocol (CSP) in more detail; any changes with regards to what is already specified in the CSP will be described in Section 6 of this document.

1.1 Study Objectives

1.1.1 Primary Objective

Primary objective:	Endpoints/variables:
To describe the pharmacokinetic (PK) parameters following a single subcutaneous (SC) administration of tezepelumab CCI in children with mild, moderate, or severe asthma	• Maximum concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve (AUC) • Terminal phase elimination half-life ($t_{1/2}$) • Apparent clearance (CL/F) • Apparent steady-state volume of distribution (V_{ss}/F)

1.1.2 Secondary Objective

Secondary objective:	Endpoints/variables:
To evaluate the immunogenicity of tezepelumab	• Presence of anti-drug antibodies (ADA)

1.1.3 Safety Objective

Safety objective:	Endpoints/variables:
To evaluate the safety and tolerability following a single SC administration of tezepelumab CCI	• Adverse events /serious adverse events • Vital signs • Laboratory parameters • Electrocardiogram (ECG)

1.1.4 Exploratory Objective

Exploratory objective:	Endpoints/variables:
CCI [redacted]	[redacted]

1.2 Study Design

This is a multicentre, open label study designed to evaluate the PK profile of tezepelumab following a single SC CCI dose in children aged ≥ 5 to 11 years with mild, moderate, or severe asthma.

Approximately 24 subjects will be enrolled and approximately 14 paediatric subjects aged ≥ 5 to 11 years (inclusive) will receive a single SC CCI dose of tezepelumab in an attempt to have at least 12 paediatric subjects complete the study. At least 4 subjects will have body weight < 25 kg and a minimum of 3 subjects will have body weight ≥ 25 kg to < 40 kg.

Subjects who are eligible to participate but do not go on to receive tezepelumab, or subjects who do not complete the required evaluations through to Day 85 may be replaced to maintain the stipulated number of evaluable subjects, at the discretion of the Sponsor.

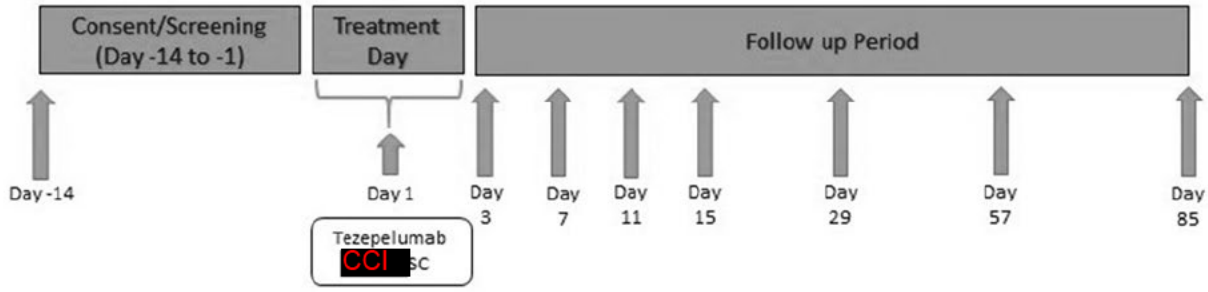
The 99-day study consists of:

- A consent/screening period of up to 14 days
- Treatment and follow-up period of 85 days.

The study design is summarised in Figure 1.

Subjects will attend the study site and informed consent will be obtained from the legal representative and informed assent will be obtained from the subject. Screening assessments should be completed within 14 days (Day -14 to Day -1). Subjects who meet eligibility criteria will receive a single SC CCI dose of tezepelumab, administered in the anterior thigh by a healthcare professional on Day 1 and remain at the study centre for 2 hours after dosing. The subjects will then return to the centre for outpatient Follow-up visits on Days 3, 7, 11, 15, 29, 57, and 85 (End of Study [EOS]). The study will be completed after the EOS visit on Day 85.

Figure 1 Study Design



1.3 Number of Subjects

No formal sample size calculation was conducted for this study. The number of subjects was based on the desire to obtain adequate PK and safety data while exposing as few paediatric subjects as possible to tezepelumab and study procedures. A total of 12 subjects treated with tezepelumab is considered sufficient to provide adequate data to characterise PK of tezepelumab in children aged ≥ 5 to 11 years. At least 4 subjects will have body weight < 25 kg and a minimum of 3 subjects will have body weight ≥ 25 kg and < 40 kg. Approximately 14 subjects will receive tezepelumab in an attempt to have at least 12 subjects complete the study.

Subjects who are eligible to participate but do not go on to receive tezepelumab, or subjects who do not complete the required evaluation through to Day 85 may be replaced to maintain the stipulated number of evaluable subjects, at the discretion of the Sponsor. In addition, subjects may be replaced when factors such as important protocol deviations are deemed to affect evaluability of subject's PK profile. Examples include, but may not be limited to, incorrect IP dose administered resulting in all PK data from the subject being unevaluable, or PK sample(s) collection missed or collected not in accordance with the protocol.

All decisions to replace a subject will be documented in a Note to Study File.

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

Analysis sets will be defined as follows.

2.1.1 Enrolled Analysis Set

This analysis set will consist of all subjects who sign the informed consent form (ICF) and will be used for reporting of overall disposition and listings including screen failures.

'Enrolled' means a subject's, and their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential

subjects who are screened for the purpose of determining eligibility for the study but are not assigned to treatment in the study, are considered 'screen failures'.

2.1.2 Safety Analysis Set

The safety analysis set will consist of all subjects who receive at least one dose of tezepelumab.

Anti-drug antibodies, PD parameter summaries and safety presentations will be based on the safety analysis set.

2.1.3 Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the Safety Analysis set that have at least one detectable tezepelumab serum concentration from a sample collected post-dose that is assumed not to be affected by factors such as important protocol deviations (e.g., incorrect dose of study IP received).

Protocol deviations that occur during the study will be considered for their severity/impact on the analysis of PK data and will be taken into consideration when subjects are assigned to the PK analysis sets.

All PK summaries will be based on the PK analysis set.

2.2 Violations and Deviations

Important protocol deviations will be defined at subject level prior to database lock (DBL) and will be tabulated and listed. In addition, a listing of all COVID-19 related protocol deviations (important and non-important) will be provided. Screen failures will not be included in above listings.

Important protocol deviations 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. The definitions of each category of important protocol deviation will be fully specified in the Protocol Deviations Management Plan (PDMP) and will include (but may not be limited to):

- subjects enrolled without fulfilling key entry criteria;
- subjects who received prohibited or restricted concomitant medications during the study;
- subjects who received the incorrect IP dose.

Important Protocol Deviations will not be a condition to exclude any subject from the safety analysis set, nor to exclude any data from subjects included in the safety analysis set.

The exclusion of any subjects from the PK analysis set, or the exclusion of selected time-points only from subjects in the PK analysis set from the calculation of the PK parameters and/or from the PK summary statistics will be documented by the PK Scientist including the reason(s) for exclusion. All exclusions will be reported in the data listings.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set will be listed only. Data excluded from subjects who are included in the PK analysis set will be excluded from summary statistics and will be listed only. However, in the event that no PK parameters can be calculated for a subject from the available data, there will not be any parameters included in a listing.

In the event that a PK sample is missing for a subject, the IQVIA Pharmacokineticist and sponsor will evaluate the PK samples collected (collection times only, not concentrations) for the subject and determine if enough samples were collected to report some or all of the protocol defined PK parameters.

The following people, at a minimum, must review the sample collection times for subjects that miss one or more PK samples to determine if a replacement subject is needed:

- Sponsor Clinical Pharmacologist or PK Specialist,
- IQVIA Pharmacokineticist.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General Principles

3.1.1 Baseline Definitions

Baseline is defined as the last valid non-missing result obtained on or prior to the date of dosing of tezepelumab.

If there is no result prior to dosing of tezepelumab, then the baseline value will not be imputed and will be set to missing.

Absolute change from baseline is defined as the difference between the relevant post-baseline value and the 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 specified otherwise, "change from baseline" is assumed to be the absolute change from baseline.

3.1.2 Study Day

Study Day will be calculated from the date of tezepelumab dosing (Day 1) and will be used to derive start/stop day of assessments and events, with the exception of concentration-time data and derived PK parameters.

If the date of the assessment/event is on or after the date of tezepelumab dosing, then:

- Study Day = (date of assessment/event – date of tezepelumab dosing) + 1.

If the date of the assessment/event is prior to the date of tezepelumab dosing, then:

- Study Day = (date of assessment/event – date of tezepelumab dosing).

3.1.3 Study Period

The following study periods are defined for analysis purposes:

- Screening period: starting on the date of obtaining informed consent/assent, and ending one day prior to IP administration.
- On-study period (treatment and follow-up): starting on the date of IP administration and ending on the study completion or date of withdrawal from study.

3.1.4 Visit Windows

Summaries and analyses for which data are presented by study day (e.g. “Day 1”) will use the analysis visit windows to classify the data record, which is derived from the assessment date relative to the date of IP administration. Study Day is defined as specified in Section 3.1.2, unless specified otherwise.

Visit window is allowed only for the visits specified in Table 1.

Table 1 Visit windows allowed

Visit	Target Day	Visit Window
V4	Day 7	4-8
V5	Day 11	9-12
V6	Day 15	13-21
V7	Day 29	22-42
V8	Day 57	43-70
V9	Day 85	71-88

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

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.

Measurements collected from unscheduled visits, repeat assessments or early study discontinuation visits may also be considered in the analysis visit window. 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 be used.

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 a subject has no value within a particular visit window, then the subject will have a missing value on that CSP scheduled study day in summaries and analysis.

3.1.5 Prior and concomitant medications

Medications or therapies will be classified per the World Health Organization (WHO) Drug Reference List dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system.

A medication will be regarded as prior if it was stopped on or before the IP dose date (medication stop date ≤ IP dose date).

A medication will be regarded as concomitant if the start date is on or after the IP dose date, but prior to the end of study period (IP dose date ≤ medication start date ≤ study completion or withdrawal date), or if it started on or prior to the IP dose date and was ongoing after the IP dose date.

The handling of partial/missing dates for prior/concomitant medications is detailed in Appendix A.

3.2 Primary Endpoints – Pharmacokinetic Parameters

The following PK parameters will be derived as primary endpoints:

• $AUC_{0\text{-}inf}$	Area under the concentration-time curve from time zero (predose) extrapolated to infinity calculated by linear up/log down trapezoidal summation and extrapolated to infinity by the addition of the last quantifiable concentration divided by the terminal rate constant
• $AUC_{0\text{-}last}$	Area under the concentration-time curve from time zero (predose) to the last measurable concentration calculated by linear up/log down trapezoidal summation
• C_{max}	Maximum observed serum concentration
• t_{max}	Time to achieve maximum observed serum concentration
• $t_{1/2}$	Terminal phase elimination half-life, calculated as $\ln(2)/\lambda_Z$ where λ_Z is the first-order rate constant associated with the terminal (log-linear) elimination phase
• CL/F	Apparent clearance, estimated as dose divided by $AUC_{0\text{-}inf}$
• V_{ss}/F	Apparent steady-state volume of distribution, estimated as CL/F*MRT, where $MRT=(AUMC_{0\text{-}inf})/(AUC_{0\text{-}inf})$.

In addition, the following PK parameter will be derived:

- V_z/F: Apparent volume of distribution (based on terminal phase), estimated as $CL/F*1/\lambda_Z$.

3.3 Secondary Endpoint – Immunogenicity

The presence or absence of ADA to tezepelumab will be determined from the blood samples collected for immunogenicity testing. A tiered testing scheme will be employed, with the first step being screening. Samples found putative positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo titre determination. Samples confirmed positive for ADA will be archived for possible testing for neutralising antibodies (nAb). A patient is defined as being ADA-positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise ADA negative.

3.4 Safety Endpoints

Safety and tolerability will be assessed in terms of AEs (including SAEs), laboratory data, vital signs, and ECGs.

3.4.1 Adverse Events

Adverse events (including SAEs) 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) at the time of database lock.

Adverse events will be categorised for analysis according to their onset date into the following study periods described in Section 3.1.3:

- AEs occurring during the screening period: date of informed consent ≤ AE onset date < date of dose of IP,
- AEs occurring during the on-study period: date of dose of IP ≤ AE onset date ≤ date of study completion or date of withdrawal from study.

If the AE has a completely missing (and unresolvable) onset date, then the AE will be considered an on-study event, 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 considered an on-study event, unless either the end date indicates unambiguously that the AE resolved before treatment started, or the imputed partial onset date is prior to start of treatment.

The handling of partial/missing dates for AEs is detailed in Appendix A.

Adverse Events of Special Interest

Certain preferred terms, groups of preferred terms, or standardised MedDRA queries (SMQs) are being identified as being of special scientific and medical interest towards improving the understanding of tezepelumab. The list of terms used to identify adverse events of special interest (AESIs) may be updated on an ongoing basis as new safety data are accumulated.

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 B.

3.4.2 Clinical Laboratory

Samples for determination of clinical chemistry, haematology, virology and urinalysis will be taken at the times detailed in Table 1 of the CSP and assessed in a central laboratory. The

parameters outlined in Table 9 of the CSP will be measured and reported in standard international (SI) units.

There will be no imputation for missing values. For values recorded with a leading greater than or less than ('>', '<') symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analysed as 0.01 and listed as <0.01.

Urinalysis data will be categorised as negative (0) or positive (+) at each visit.

The investigator will assess the available lab results with regards to clinically relevant abnormalities. Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory reference ranges that will be used will follow the most recent version of the AZ standard reference ranges and unit conversion external data. All absolute values falling outside the AZ provided reference ranges will be flagged in the listings. These classifications will also be used for shift tables.

For the purpose of shift tables, baseline will be defined as specified in Section 3.1.1. Maximum or minimum value post-baseline will be calculated over the entire post-baseline period.

For the liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin (TBL), the multiple of the central laboratory upper limit of the normal (ULN) range will be calculated for each data point:

Multiple = Value / ULN,

i.e. if the ALT value was 72 and the ULN 36, then the multiple would be 2.

3.4.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, weight, height, Body mass index (BMI), respiratory rate and body temperature) will be assessed.

Vital sign results will be compared to the given reference ranges (Table 2) and classified as low (below range), normal (within range or on limits) or high (above range). All results falling outside the reference ranges will be flagged in the listings. The investigator will assess the results with regards to clinically relevant abnormalities. In addition, changes in vital signs between baseline and each subsequent scheduled assessment will be calculated.

Table 2 Vital Signs Reference Ranges for Age 5-11 Years

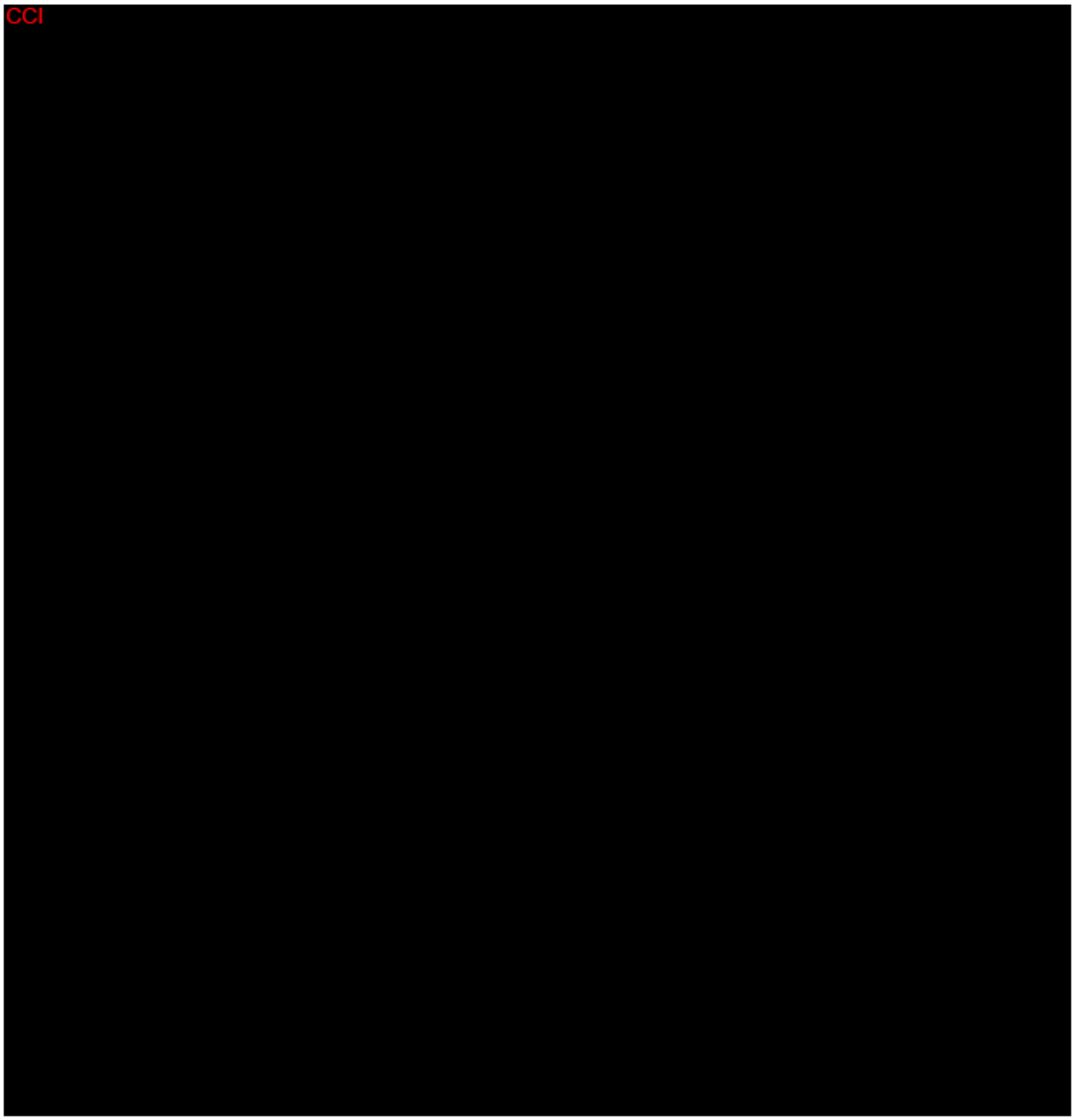
Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure	mmHg	57	80
Systolic Blood Pressure	mmHg	97	120
Pulse Rate	bpm	70	110
Respiratory Rate	breaths/min	20	30
Body Temperature	°C	35.5	37.5
Weight	kg	15	NA

3.4.4 Electrocardiograms

A 12-lead ECG will be performed at timelines as specified in Table 1 of the CSP, using local site equipment after at least 5 minutes of rest for the subject in a quiet setting without distractions.

The outcome of the investigator's overall ECG evaluation will be recorded as normal/abnormal in the CRF and with any abnormalities recorded as not clinically significant or clinically significant.

CCI



4 ANALYSIS METHODS

4.1 General Principles

The analyses will be performed by IQVIA using the SAS® (Statistical Analysis Software; SAS Institute, Inc., Cary, North Carolina) statistical software system version 9.4 or higher. All analyses will be performed according to AZ standard operating procedures unless otherwise stated herein.

After the last subject has completed their Visit 9, the database for the study will be locked and the data will be reported in a CSR.

All individual data as recorded in the final study database, after the last subject has completed their Visit 9, will be provided by IQVIA Data Management.

No formal statistical hypothesis tests will be made. Data will be provided in data listings sorted by subject number. Tabular summaries will be presented.

For qualitative variables and categorical data, the population size (N), number of patients with available data (n) , and the percentage (of available data) for each class of the variable will be presented. Percentages will be rounded to 1 decimal place.

Quantitative data, including PK data, will be summarised using descriptive statistics, including N, n, mean, standard deviation (SD), 1st quartile (Q1), median, 3rd quartile (Q3), minimum (min), and maximum (max), unless stated otherwise.

Additionally, coefficient of variation (CV%), geometric mean, geometric SD, and geometric coefficient of variation (GCV%) will be reported for PK concentrations and parameters, except t_{max} which will be summarized using n, median, min and max. These results will be presented in tables and figures as applicable.

Geometric mean is calculated as exp[μ], where μ is the mean of log-transformed data.

GCV% is calculated as $100\sqrt{[\exp(s^2)-1]}$, where s is the SD of log-transformed data.

For non-PK data the mean, median, and first and third quartiles (where applicable) will be presented with one more decimal place than the raw data, the SD will be presented with two more decimal places than the raw data, and min and max values will have the same number of decimal places as the raw data.

For all serum concentrations and PK parameters for tezepelumab, data and descriptive statistics will be presented in summary tables and by-subject listings as described in Table 3, but the calculation of summary statistics will be performed using unrounded data.

Table 3 Conventions for Reporting of Pharmacokinetic Data

Variable/ Parameter	Data in Listings	Reporting in Summary Tables			
		Geometric Mean	Mean, SD, Median	Min, Max	CV%, GCV%
Serum concentrations	AR, up to 4 dp	AR+1, up to 4dp	AR+1, up to 4dp	AR, up to 4 dp (a)	1dp
$AUC_{0\text{-}inf}$	3sf	3sf	3sf	3sf	3sf
$AUC_{0\text{-}last}$	3sf	3sf	3sf	3sf	3sf
C_{max}	3sf	3sf	3sf	3sf	3sf
t_{max}	2dp	NA	Median 2dp	2dp	NA
$t_{1/2}$	3sf	3sf	3sf	3sf	3sf
CL/F	3sf	3sf	3sf	3sf	3sf
V_{ss}/F	3sf	3sf	3sf	3sf	3sf
V_z/F	3sf	3sf	3sf	3sf	3sf
λ_z	4sf	4sf	4sf	4sf	4sf

NA Not applicable; sf Significant figures; dp Decimal places; AR As Reported
(a) AR except in the scenario where ½ LLOQ is the min; refer to Section 4.2.4.2.
(b) Serum concentrations will be converted to µg/mL for the listings and summary statistics.
(c) Time variables will be converted to days.

The treatment will be labelled in the relevant PK, PD, and safety summaries and data listings as "Tezepelumab CCI SC".

4.2 Analysis Methods

4.2.1 Demographics and Baseline Characteristics

4.2.1.1 Subject Disposition

Subject disposition will be summarised using all enrolled subjects (enrolled analysis set). Percentages will be calculated based on the number of subjects assigned to treatment.

The number of subjects enrolled, and the number and percentage of subjects received study treatment, did not receive study treatment, completed study, and prematurely withdrawn from study (including reason) will be presented. Study discontinuation reasons are detailed in CSP Section 7.2. The number of subjects withdrawing from study due to pandemic or other global country situations will be summarised as well. Reasons for prematurely withdrawing from study will also be listed.

A listing of all subjects impacted by pandemic or other global country situations disruptions will be produced with details of changed or missed visits.

The number and percentage of subjects included and excluded from each analysis set will be summarised, including the reason for exclusion from each analysis set. Important protocol

deviations will also be provided in a separate table and listed for the safety analysis set. In addition, a listing of all COVID-19 related protocol deviations (important and non-important) will be provided.

4.2.1.2 Demographics and Other Baseline Characteristics

Demographics and subject characteristics will be summarised using frequencies and percentages (for categorical variables sex, race and ethnic group) and descriptive statistics (for continuous variables age, height, weight and BMI) using both the PK and safety analysis set.

Various baseline characteristics will also be summarised for all subjects in the safety analysis set. These include relevant medical and surgical histories, spirometry lung function data at screening such as CCI [redacted] at baseline, and respiratory disease characteristics including asthma duration, age at onset of asthma, the number of exacerbations in the previous 6 months, and the number of exacerbations requiring hospitalisations in the previous 6 months.

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

4.2.2 Prior and Concomitant Medications

The number and percentage of subjects taking maintenance asthma medications such as ICS/ long acting beta agonist (LABA) fixed dose combinations, at baseline will be summarised. For those subjects taking ICS at baseline the converted dose units will also be summarised. The details concerning dose conversions for ICS are provided in the Appendix H of the CSP. The number of subjects treated with ICS at baseline will be summarised by ATC code and preferred term, with total daily dose (non-converted) at baseline summarised for each preferred term.

Disallowed medications will include medications defined as prohibited according to Section 6.5.2 of the CSP. They will be defined following a physician review (prior to database lock) of the unique combinations of Anatomical Therapeutic Chemical (ATC) code classifications and generic terms captured.

Separate tables will be presented for all allowed and disallowed medications received during each of the following study periods: screening period and on-study period respectively.

Prior and concomitant medications will be listed for the safety analysis set, including allowed and disallowed medications.

4.2.3 Exposure to Investigational Product

The number and percentage of subjects who received IP will be summarised. Exposure data will be summarised and listed for the safety analysis set.

4.2.4 Pharmacokinetics

All PK analyses will be based on the PK analysis set.

4.2.4.1 Handling of Missed PK Sample Collections

Data from subjects that have missing PK sample(s) will be included in concentration-time listings, individual PK profile plots and associated summary statistics. Available PK parameters will be included in the PK parameter listing and associated summary statistics.

4.2.4.2 Serum Concentration Data

All tezepelumab serum concentration data received will be listed by subject, and summaries will be presented by nominal time in days (calculated as Study Day minus 1), for subjects included in the PK analysis set. A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. The individual serum tezepelumab concentrations will be plotted versus actual elapsed time of PK sampling relative to dosing time in days; the geometric mean (together with confidence intervals derived as geometric mean multiplied or divided by geometric SD) of serum tezepelumab concentrations will be plotted versus nominal time; the y-axis will be presented on both a linear and a log-scale.

Serum concentrations below the lower limit of quantification (LLOQ) will be handled as follows for descriptive statistics:

- At a time point where 50% or less of the values are below the LLOQ (BLQ), all BLQ values will be set to ½ LLOQ, and all descriptive statistics will be calculated. The maximum value will be reported from the individual data, and the minimum will be reported as ½ LLOQ.
- At a time point where more than 50%, but not all, of the values are BLQ, the mean, SD, geometric mean, and CV% will be reported as 'Not Determined' (ND). The maximum value will be reported from the individual data, and the minimum and median will be reported as BLQ.
- If all the concentrations are BLQ, the geometric mean and mean, and the minimum, median, and maximum will be reported as BLQ, and the SD, CV%, and GCV% as ND.
- The number of BLQ values (n below LLOQ) will be reported for each time point.

4.2.4.3 Pharmacokinetic Parameters

Any BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the profile. BLQ values that occur at any other time points are treated as missing and excluded from the PK analysis for the calculation of PK parameters.

If two or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values will be excluded

from the PK analysis for the calculation of PK parameters, unless otherwise warranted by the concentration-time profile.

The following PK parameters will be estimated, if appropriate, using noncompartmental analysis method performed using WinNonlin® version 8.0 or higher. The actual elapsed sampling times will be used in the final PK parameter calculations. A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters.

The following PK parameters, as appropriate based on the data, will be listed by subject and summarised using descriptive statistics:

- $AUC_{0\text{-}inf,}$
- $AUC_{0\text{-}last,}$
- C_{max},
- t_{max},
- $t_{1/2,}$
- CL/F,
- V_{ss}/F,
- V_Z/F.

The following PK parameters will be calculated for diagnostic purposes and listed but not summarised:

- λ_Z, N — Number of data points included in the log-linear regression analysis to determine λ_Z. A minimum of 3 data points will be used for determination.
- Rsq — Goodness of fit statistic for calculation of λ_Z. If the Rsq is <0.800, then λ_Z and related parameters will be flagged.
- Tlast — Time of the last postdose quantifiable serum concentration.
- %AUCex — Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation, calculated as $[(C_{last}/\lambda_Z)/AUC_{0\text{-}inf}*100]$. If the %AUCex is greater than 30.0% of $AUC_{0\text{-}inf}$, then $AUC_{0\text{-}inf}$ and related parameters will be flagged.

Note: parameters will be included in summary statistics unless they are deemed necessary to exclude due to protocol deviations. The PK data obtained in this study may be included in a population PK analysis, as appropriate, to assess any PK differences between children aged ≥ 5 to 11 years and adults/adolescents, and guide dosing for future studies of tezepelumab in paediatric subjects. If conducted, this analysis will be reported separately from the CSR.

Day 29 PK analysis results will be evaluated after last subject has completed their visit on Day 29 (Visit 7) to confirm the dose of tezepelumab selected for future safety and efficacy study in 5 to <12 years old children.

4.2.5 Immunogenicity

All listings and summaries of ADA results will be based on the safety analysis set. Immunogenicity of tezepelumab (ADA) results will be listed by subjects with any positive ADA result at any time first, followed by subjects with no positive ADA result by scheduled visit. The corresponding titre summaries (e.g. 1st quartile, median, 3rd quartile) of each ADA category will be provided, and will be based on the maximum titre of all positive samples for each subject.

The ADA status across the study for each subject will also be classified and listed as per the following categories:

- Subjects who are ADA positive at any time including baseline and/or post-baseline (ADA prevalence).
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive at baseline and positive in at least one post baseline measurement.
- Subjects who are ADA positive at baseline regardless of post-baseline result.
- Subjects who are ADA positive post-baseline.
- Subjects who are ADA positive post-baseline and ADA negative at baseline (treatment induced ADA positive)
- Subjects who are treatment boosted ADA positive, defined as baseline positive ADA titre that was boosted to a 4 fold or higher level following IP administration
- Subjects who are treatment emergent ADA (TE-ADA) positive (ADA incidence): defined as either treatment induced ADA positive or treatment boosted ADA positive.

4.2.5.1 Potential effects of ADA on PK

The impact of ADA on PK will be explored using the PK analysis set.

The impact of ADA on PK will be explored by comparing individual serum tezepelumab concentration time profiles in ADA positive (any time) and ADA negative subjects.

4.2.5.2 Potential effects of ADA on Safety

Impact of ADA on AEs may be evaluated as appropriate.

4.2.6 Safety

All safety and tolerability variables will be summarised and evaluated descriptively using the safety analysis set. Out-of-range values for safety laboratory and vital signs (based on paediatric reference values provided in Table 2 of SAP) will be flagged in individual listings.

Safety data will be reported using the safety analysis set. Safety data will be presented using descriptive statistics unless otherwise specified.

4.2.6.1 Adverse Events

All AEs experienced by the subjects will be collected throughout the study, as per CSP Table 1, and will be coded by IQVIA using the latest version of MedDRA at the time of database lock.

Adverse events and SAEs will be categorised for analysis according to their onset date into occurring during the screening period or the on-study period. Adverse events occurring during the screening period will only be presented in the subject listing. Adverse events occurring during the on-study period will be summarised and listed as follows:

An overall summary table will be produced showing the number and percentage of subjects with at least one AE in each of the following categories: any AEs, SAEs, AEs with outcome of death, and AEs leading to withdrawal from study. The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e. accounting for multiple occurrences of the same event in a subject).

Adverse events, SAEs, AEs with outcome of death, AESIs and AEs leading to withdrawal from study will be summarised by SOC and PT assigned to the event using the MedDRA dictionary by descending frequency order. 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).

Adverse events and SAEs will be summarized by PT and Investigator's causality assessment (related versus not related) and maximum intensity. If a subject reports multiple occurrence of the same AE within the same reported period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being severe, moderate, and mild).

Separate listings of subjects with AEs, SAEs, AEs with outcome of death and AEs leading to withdrawal from study will be presented.

4.2.6.2 Clinical Laboratory

All continuous laboratory parameters will be summarised descriptively by absolute value by each planned visit, together with the corresponding changes from baseline using the safety analysis set. These summaries will be produced for baseline and all scheduled post-baseline visits. All variables will be summarised in SI units.

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

In order to identify potential Hy's Law cases, maximum post-baseline TBL will be presented (<2 and ≥2xULN) against maximum post-baseline ALT (<3, ≥3 - <5, ≥5-<10, and ≥10 x ULN), expressed as multiples of ULN. This will be repeated to show maximum post-baseline TBL against maximum post-baseline AST. Maximum post-baseline TBL will also 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.

A shift table will also be provided for each urinalysis qualitative assessment using the number and percentage of subjects with baseline results of negative or positive versus the maximum post-baseline result of negative or positive.

Any data outside the laboratory reference ranges will be flagged and explicitly noted on the listings that are produced.

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

4.2.6.3 Vital Signs

All vital signs variables, including systolic blood pressure, diastolic blood pressure, pulse rate, weight, height, body mass index (BMI), respiratory rate and body temperature, will be summarized by absolute value at each visit using the safety analysis set, together with the corresponding changes from baseline. These summaries will be produced for baseline and all scheduled post-baseline visits.

The normal reference ranges listed in Table 2 will be used for the identification of individual abnormalities. A shift table will be produced for each vital sign variable (Diastolic Blood Pressure, Systolic Blood Pressure, Pulse Rate, Respiratory Rate, Body Temperature) to display low, normal, and high values. The shift tables will present baseline and maximum/minimum post-baseline values for each variable. Additionally, the incidence of clinically notable vital signs abnormalities, as judged by the investigator, will be summarised.

All recorded vital signs data will be listed.

4.2.6.4 Electrocardiograms

The outcome of the overall investigator ECG evaluation recorded as normal or abnormal with any abnormalities recorded as not clinically significant or clinically significant will be listed for all subjects by safety analysis set.

Abnormal values will not be recorded as AEs unless deemed clinically significant.

A summary table will be produced for ECG evaluations at baseline and all scheduled post-baseline visits to display normal, abnormal – not clinically significant, abnormal – clinically significant and not done.

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5 INTERIM ANALYSES

No formal interim analyses are planned in this trial.

6 CHANGES OF ANALYSIS FROM PROTOCOL

In the change to the protocol, Day 29 PK analysis results will be evaluated to confirm the dose of Tezepelumab selected for the future safety and efficacy study in 5 to <12 years old children.

7 REFERENCES

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Juniper EF. Paediatric asthma quality of life questionnaires (PAQLQ, PAQLQ(S), MiniPAQLQ and PACQLQ): Background, administration and analysis. 2006; QOL Technologies Ltd., Bosham, UK.

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Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005; 26:319-38.

8 APPENDIX

Appendix A Handling Incomplete Dates for Adverse Events and Medications

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify on-study AEs and to classify prior and concomitant medications.

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation. In instances where imputed values will be presented, impute values will be flagged.

Adverse Events

- The missing day of onset of an AE will be set to:
  - First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of IP dosing
  - The day of IP dosing, if the onset YYYY-MM is the same as YYYY-MM of IP dosing
  - The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of IP dosing.
- The missing day of resolution of an AE will be set to:
  - The last day of the month of the occurrence. If the subject died in the same month, then set the imputed date as the death date.
- If the onset date of an AE is missing both the day and month, the onset date will be set to:
  - January 1 of the year of onset, if the onset year is after the year of IP dosing.
  - The date of IP dosing, if the onset year is the same as the year of IP dosing.
  - The date of informed consent, if the onset year is before the year of IP dosing.
- If the resolution date of an AE is missing both the day and month, the date will be set to:
  - December 31 of the year of occurrence. If the subject died in the same year, then set the imputed date as the death date.

Prior/concomitant medication

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify prior/concomitant medications:

- The missing day of start date of a therapy will be set to the first day of the month of the occurrence.
- The missing day of end date of a therapy will be set to the last day of the month of the occurrence.

- If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of occurrence.
- If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.
- If the start date of a therapy is null and the end date is not a complete date, then the start date will be set to the date of the first study visit.
- If the start date of a therapy is null and the end date is a complete date:
  - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
  - otherwise the start date will be set to the end date of the therapy.
- If the end date of a therapy is null and the start date is not a complete date, then the end date will be set to the date of the last study visit.
- If the end date of a therapy is null and the start date is a complete date:
  - and the start date is prior to the date of the last study visit then the end date will be set to the date of the last study visit.
  - otherwise, the end date will be set to the start date of the therapy.

Appendix B Preferred Terms for Adverse Events of Special Interest

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.

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.

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.

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.

Severe infections (as defined in the protocol)

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

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

- "AE Category" on Adverse Events eCRF page marked as "Severe Infection", and one or more of the following:
  - AE is serious ("Serious" on Adverse Events eCRF page marked as "Yes"), or
  - AE required treatment with systemic antiviral medications, intravenous antibiotics or medications for Helminth parasitic infection.

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".

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.

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.

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