STATISTICAL ANALYSIS PLAN	
Study Code	D5180C00031
Edition Number	2.0
Date	24-Mar-2022

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Potential Effect of Tezepelumab on the Humoral Immune Response to Seasonal Quadrivalent Influenza Vaccination in Adolescent and Young Adult Participants with Moderate to Severe Asthma (VECTOR)

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
CCI	[redacted]
ADA	Anti-Drug Antibody
AE	Adverse event
AESIs	AEs of special interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CIs	Confidence Intervals
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
ECG	Electrocardiogram
EOT	End of Treatment
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCV	Geometric Coefficient of Variation
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
HAI	Hemagglutination-Inhibition
IPD	Important Protocol Deviation
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
nAb	Neutralizing Antibodies
NC	Non-Calculable
NQ	Non-Quantifiable

Abbreviation or Specialized Term	Definition
PD	Protocol Deviation
PK	Pharmacokinetics
PT	Preferred Term
SAE	Serious AEs
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
ULN	Upper Limit of Normal

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	08/11/2021	Initial approved SAP	N/A	N/A
Primary endpoint(s)	24/03/2022	Language relating to primary and final database locks was added.	Yes (V3)	To add primary analysis of data at Visit 7 (Week 16).
Data presentation	24/03/2022	Vaccine immunogenicity analysis set population updated to exclude participants who experience an influenza infection prior to Visit 7 (Week 16) assessments.	Yes (V3)	To reduce the potential to interfere with the generation or interpretation of an antibody response.
Data presentation	24/03/2022	Updated from 'Visit' to 'Week' throughout for data presentation.	Yes (V3)	Displaying as 'week' is more clear and aligns with other studies.
Other	24/03/2022	Added language to describe when unblinding will occur.	Yes (V3)	To clarify when unblinding will occur in relation to the primary analysis.
Other	24/03/2022	Updated appendix B to add further rules on partially missing concomitant medication dates.	N/A	

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D5180C00031. This study is a Phase 3b, multicenter, randomized, double-blind, parallel group, placebo-controlled study investigating the potential effect of tezepelumab on antibody responses following seasonal quadrivalent influenza virus vaccination. The reader is referred to the clinical study protocol (CSP) and the case report form (CRF) for details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Pre- and post-dose wording in CSP was updated to pre- and post-vaccination in the statistical analysis plan (SAP), when referring to the influenza vaccine.

Hypersensitivity reactions was added as an AESI in Appendix 7.3.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

There is neither an unblinded data review nor interim analysis planned for this study prior to primary database lock. There will be two database locks in this study. The primary database lock and analysis will be conducted after the last participant (enrolled in the 2021/2022 flu season) completes Visit 7 (Week 16), and the final database lock and analysis will be conducted once all participants have completed the follow-up period, Visit 8 (Week 28). All analyses of the primary objectives and selected safety objectives will be performed based on the primary database lock data.

3.2 Analysis Populations

Antibody endpoints to the influenza vaccine—strain-specific hemagglutination-inhibition (HAI) and microneutralization (MN) antibody geometric mean fold rises (GMFRs) and geometric mean titers (GMTs)—will be analyzed using the vaccine immunogenicity analysis set. All remaining efficacy analyses will be performed using an Intent-to-Treat (ITT) approach based on the Full analysis set. Demographic and baseline characteristics will be presented for the Full analysis set, and separately for the Vaccine immunogenicity analysis set if the difference between the number of participants in the two analysis sets is >=5%. Safety objectives and anti-drug antibody (ADA) summaries will be analyzed based on the Safety analysis set. The population analysis sets are defined in Table 1.

Table 1 Populations for Analysis

Population/ Analysis set	Description
All participant analysis set	All participants screened for the study will be included in the 'All participant analysis set' and will be used for reporting of disposition and screening failures.
Full analysis set	All participants randomized and receiving any study intervention will be included in the 'Full analysis set', irrespective of their CSP adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Participants who withdraw informed consent/assent to participate in the study will be included up to the date of their study termination.
Vaccine immunogenicity analysis set	All randomized participants who received the influenza vaccine plus at least 1 dose of tezepelumab or placebo, had pre- and post-vaccination HAI or MN antibody measurements, had no influenza infection prior to Visit 7 (Week 16), and had no protocol deviation, judged to have the potential to interfere with the generation or interpretation of an antibody response, will be included in the 'vaccine immunogenicity analysis set'. The analyses conducted using this analysis set will be based on the actual treatment received. Protocol deviations (PDs) will be specified in the PD specification and reviewed by the study team before unblinding at the primary database lock (Visit 7 [Week 16]).
Safety analysis set	All participants who received at least 1 dose of study intervention will be included in the 'safety analysis set'. Participants will be classified according to the treatment they actually received. A participant who has on one or several occasions received active treatment will be classified as active. All safety and ADA summaries will be based on this analysis set.
Pharmacokinetic (PK) analysis set	All participants who received tezepelumab and from whom PK blood samples were obtained and assumed not to be affected by factors such as CSP deviations will be included in the 'PK analysis set'. Those participants who had at least 1 quantifiable serum PK observation post first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

Abbreviations: ADA=anti-drug antibody; CSP=clinical study protocol; HAI=hemagglutination-inhibition; ITT=intent to treat; MN=microneutralization; PD=protocol deviation; PK=pharmacokinetic.

3.3 General Considerations

All statistical analyses will be performed by Parexel International, under the direction of the Late Stage Respiratory and Immunology Biometrics Group, AstraZeneca. All statistical analyses will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, US), version 9.4 or higher.

All personnel involved with the analysis and conduct of the study will remain blinded until the primary database lock and important protocol deviations, have been identified. After the primary database lock, treatment allocation for participants during this study will become known to the sponsor staff and designated CRO. The blind will be maintained for the investigator, investigational site staff, and for the participant.

3.3.1 General Study Level Definitions

Unless stated otherwise, continuous variables will be summarized by descriptive statistics (number of participants [n], arithmetic mean, standard deviation (SD), minimum, median and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Mean(s), median(s), SD(s) and quartiles (where applicable) will be displayed with one more decimal place than the collected data. Minimum(s) and maximum(s) will be displayed with the same number of decimal places as the collected data. For discrete variables, population size (N for analysis set size and n for available data) and percentage will be presented. Percentages will be displayed with one decimal place.

As no statistical testing is planned, no p-values will be presented.

If influenza vaccine administration is delayed, an additional one to two study intervention doses may be administered to participants during unscheduled visits prior to visit 6 (as needed) until the influenza vaccine is available at study sites. Throughout this document End of Treatment (EOT) refers to the end of treatment visit, which is four weeks after the last dose of study intervention and could be either week 16, 20 or 24 for each participant. The end of study visit is 16 weeks after last dose of study intervention.

3.3.2 Visit Window

All summaries and analyses which are presented by visit will use the nominal visit label. This will allow for correct classification of Visit 6 (pre-vaccination antibody measure), Visit 7 (EOT), and Visit 8 (End of Study) at different time points for different participants due to influenza vaccination delay should it occur, as described in section 3.3.1.

Participants who discontinue study intervention early should attend all further study visits as defined in the CSP, hence any collected data will be used as planned.

3.3.3 Handling of Unscheduled Visits

All assessments during the unscheduled visits, due to delayed influenza vaccine administration, may not necessarily be completed. All available data will be included in analyses.

3.3.4 Multiplicity/Multiple Comparisons

The statistical analysis of each of the four primary variables will be performed separately for each strain and separately for both HAI and MN antibody titers; except for the Influenza A H3N2-strain, where only the MN assay will be performed owing to the known low hemagglutination effect of the strain (Sicca et al 2020). No adjustment of multiplicity will be performed.

The secondary endpoint variables will be summarized using descriptive statistics.

3.3.5 Handling of Protocol Deviations in Study Analysis

Only important protocol deviations (IPDs) will be listed and tabulated, and only for randomized participants (i.e. 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 participant's rights, safety or well-being. They may include (but not be limited to):

- Participants who were randomized even though they did not meet key inclusion criteria or who met at least one key exclusion criteria
- Participants who met discontinuation criteria for study treatment but were not withdrawn from study treatment
- Participants who developed withdrawal criteria during the study but were not withdrawn
- Participants who received the wrong treatment or an incorrect dose
- Participants who received a restricted or prohibited concomitant treatment.

All PDs will be listed and identified as important or non-important in the PD specification. All IPDs will be identified and documented by the study team prior to unblinding of the trial at primary database lock. The occurrence of IPDs will be monitored, in a blinded fashion during the trial, with the emphasis on their future prevention.

Except for the vaccine immunogenicity analysis set and PK analysis set, PDs including important PDs, will not be used to exclude any participant from any analysis set, nor to exclude any data from participants included in an analysis set.

Any PDs which are not defined as important, except Coronavirus disease 2019 (COVID-19) related PDs, will not be reported or discussed in the Clinical Study Report (CSR).

3.3.6 Definition of baseline

In general, the last non-missing measurement on or prior to the date of randomization will serve as the baseline measurement for efficacy variables. If there is no value on or prior to the date of randomization, 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.

3.3.7 Change from baseline

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 change from baseline will also be missing.

4 STATISTICAL ANALYSIS

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

4.1 Study Population

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

4.1.1 Patient Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Screen failures are defined as participants who complete informed consent/assent to participate in the clinical study but are not subsequently randomly assigned to study intervention.

4.1.1.2 Presentation

Participant disposition will be summarized using the all participants analysis set. The number of participants screened will be summarized. The number and percentage of participants within each treatment group will be presented by the following categories: randomized, randomized but not treated (and reason), started treatment, completed treatment, discontinued treatment (and reason), completed study, and withdrawn from study. Participant recruitment by center will also be summarized.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

See section 0 for full definitions of the analysis sets.

4.1.2.2 Presentation

The number and percentage of participants in each of the analysis sets will be summarized by treatment group, along with reason for exclusion for participants not included in each set. Refer to Table 1 Populations for Analysis for full definitions of each analysis sets.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

See section 3.3.5 for definition of IPDs.

4.1.3.2 Presentation

IPDs will be summarized for the full analysis set, by treatment group and overall. All COVID-19 related IPDs will be summarized together with all non-COVID-19 related IPDs, along with an additional summary of IPDs related to COVID-19, and IPDs excluding COVID-19 related IPDs separately.

A listing of all COVID-19 related PDs (important and non-important PDs) will be provided.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic data will include age at time of informed consent, sex, race, and ethnicity. Age will be summarized both continuously and by group, split by the stratification factors: >=12 to <18 and >=18 to <=21.

4.1.4.2 Presentation

Demographics will be summarized by treatment group and presented for the full analysis set, and the vaccine immunogenicity analysis set if applicable, as detailed in section 0.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics (weight [kg], height [cm], and body mass index (BMI) [kg/m^2]) are collected at visit 1.

4.1.5.2 Presentation

Baseline characteristics will be summarized by treatment group and presented for both the full analysis set and the vaccine immunogenicity analysis set if applicable, as detailed in section 0.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics will include, but is not limited to; smoking status, history of allergy, asthma medications, the number of asthma exacerbations in the previous 12 months, number of asthma exacerbations requiring hospitalizations in the previous 12 months, and CCI [redacted].

Baseline lung function is collected at either visit 1 or visit 2, and is assessed for both pre- and post-bronchodilator spirometry. Measures include Forced Vital Capacity (FVC) (L), FVC (%), Forced Expiratory Volume in 1 second (FEV1) (L), FEV1 (% of predicted normal), FEV1 reversibility (L), FEV1 reversibility (%), and FEV1/FVC Ratio (%). Historical reversibility will be listed, where available.

4.1.6.2 Presentation

Disease characteristics will be summarized by treatment group and presented for both the full analysis set and the vaccine immunogenicity analysis set if applicable, as detailed in section 0.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical histories are reported at screening.

4.1.7.2 Presentation

Medical and surgical histories will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA, and will be presented for the full analysis set.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

A list of permitted, restricted and prohibited medications can be found in section 6.5 of the CSP. Please refer to Appendix B: Imputation Rules for Missing/Partially Missing Prior/Concomitant Medication for the method of imputation of missing concomitant medication onset/start and end/stop dates.

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

- Prior medications:
  - end date ≤ date of first dose of study intervention
- Concomitant medications during on-treatment period:
  - end date > date of first dose of study intervention and start date ≤ minimum (date of last dose of study intervention + 33 days, date of death, date of study withdrawal), or
  - end date ongoing and start date ≤ minimum (date of last dose of study intervention + 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 study intervention + 33 days.

4.1.8.2 Presentation

Prior, concomitant and disallowed medications will be summarized by their Anatomical Therapeutic Chemical (ATC) classification system codes and generic name, by treatment group. Each will be presented for the full analysis set. On-treatment and post-treatment concomitant medications will be summarized separately.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance will be calculated as follows:

$$Treatment\ compliance\ (\%) = \left(\frac{\text{total number of actual dosing occasions}}{\text{total number of expected dosing occasions}}\right) \times 100$$

In order to allow for participants who discontinue study intervention early or who receive additional doses due to delayed flu vaccine administration, in the compliance calculation, the number of expected dosing occasions will be calculated as the number of dosing visits up to and including the last available dosing visit for that participant.

4.1.9.2 Presentation

Treatment compliance will be summarized by treatment group and presented for the full analysis set. The date and time of study intervention administrations, and all missed doses will be listed.

4.2 Endpoint Analyses

This section covers details related to the efficacy endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses. Table 2 gives details of the primary analysis estimands.

Table 2 Primary Analysis Estimands and Endpoints

Primary Endpoints	Parameters
• Post-vaccination strain-specific HAI antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT) • Post-vaccination strain-specific MN antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT) • Post-vaccination strain-specific serum HAI antibody GMTs obtained at Week 16 (EOT) • Post-vaccination strain-specific serum MN antibody GMTs obtained at Week 16 (EOT)	**Population:** Vaccine immunogenicity analysis set, defined as all randomized participants who received the influenza vaccine plus at least 1 dose of tezepelumab or placebo, had pre-vaccination and post- vaccination HAI or MN antibody measurements, had no influenza infection prior to Visit 7 (Week 16), and had no protocol deviation judged to have the potential to interfere with the generation or interpretation of an antibody response. **Intercurrent Events:** Treatment discontinuation: All data up to timepoint of post-vaccination antibody measurements will be included for participants in the vaccine immunogenicity analysis set. Initiation of any other medication: All data up to timepoint of post-vaccination antibody measurements will be included for participants in the vaccine immunogenicity analysis set. **Summary Measure:** Least square geometric mean ratio estimates for placebo vs. tezepelumab and corresponding 90% confidence intervals (CIs).
• Post-vaccination strain-specific antibody response at EOT with antibody response defined as a ≥ 4-fold rise in HAI antibody titer from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT) • Post-vaccination strain-specific antibody response at EOT with antibody response defined as a ≥ 4-fold rise in MN antibody titer from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT) • Post-vaccination strain-specific HAI antibody titer ≥ 40 at Week 16 (EOT) • Post-vaccination strain-specific MN antibody titer ≥ 40 at Week 16 (EOT)	**Population:** Vaccine immunogenicity analysis set, defined as all randomized participants who received the influenza vaccine plus at least 1 dose of tezepelumab or placebo, had pre-vaccination and post-vaccination-dose HAI or MN antibody measurements, had no influenza infection prior to Visit 7 (Week 16), and had no protocol deviation judged to have the potential to interfere with the generation or interpretation of an antibody response. **Intercurrent Events:** Treatment discontinuation: All data up to timepoint of post-vaccination antibody measurements will be included for participants in the vaccine immunogenicity analysis set. Initiation of any other medication: All data up to timepoint of post-vaccination antibody measurements will be included for participants in the vaccine immunogenicity analysis set. **Summary Measure:** Number and % of participants in each treatment group meeting the specified threshold and corresponding 90% CI.

4.2.1 Primary Endpoint

4.2.1.1 Definition

The primary objective is to evaluate the effect of tezepelumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult participants with moderate to severe asthma.

The primary endpoints are defined as follows:

- Post-vaccination strain-specific HAI antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT).
- Post-vaccination strain-specific MN antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT).
- Post-vaccination strain-specific serum HAI antibody GMTs obtained at Week 16 (EOT).
- Post-vaccination strain-specific serum MN antibody GMTs obtained at Week 16 (EOT).
- Post-vaccination strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in HAI antibody titer from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT).
- Post-vaccination strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in MN antibody titer from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT).
- Post-vaccination strain-specific HAI antibody titer ≥ 40 at Week 16 (EOT).
- Post-vaccination strain-specific MN antibody titer ≥ 40 at Week 16 (EOT).

As the HAI assay may not work for one of the influenza virus strains (Influenza A H3N2), the corresponding MN result for that strain will only be used, please see CSP for more details on the influenza virus strains. Hence, both the HAI and MN results will serve as the dual primary endpoints for this study such that results from both assays can be used for the analyses of the primary objective. This dual endpoint approach allows for a broader characterization of the immune response and flexibility in case the results for either assay are missing. The analyses of the primary endpoints will be summarized separately for each influenza virus strain, using the vaccine immunogenicity analysis set.

4.2.1.2 Derivations

Geometric mean fold rises for the HAI and MN antibody measurements are defined as:

$GMFR = \text{antilog}_e (\text{mean} [\log_e x])$

Where x is the post-vaccination (EOT) HAI or MN antibody titer fold rise from Week 12 (pre-vaccination antibody measure) and e is the natural logarithm.

Geometric mean titers for the HAI and MN antibody measurements are defined as:

GMT = antilog$_e$ (mean [log$_e$ y])

Where y is the HAI or MN antibody titer and e is the natural logarithm.

For HAI & MN assay results reported as lower than the lower limit of quantification (LLOQ), a value equal to half of the LLOQ will be imputed and used for analysis purposes.

4.2.1.3 Handling of Dropouts and Missing Data

If informed consent/assent to the study was withdrawn, all data up until the date of withdrawn informed consent/assent will be included.

4.2.1.4 Primary Analysis of Primary Endpoint

Geometric mean fold rises and GMTs will be summarized by influenza virus strain and treatment group, and the least square geometric mean ratio of GMFRs and GMTs between treatment groups (influenza vaccine divided by tezepelumab and influenza vaccine) will be calculated via an analysis of covariance (ANCOVA) model on the log-transformed variable, adjusting for treatment group and age stratum (adolescents aged 12 to 17 or young adults aged 18 to 21). The least square geometric mean ratio and mean difference will be provided with associated 90% CIs. The results of this analysis will also be presented in forest plots.

The antibody response to the influenza vaccine is defined as a ≥ 4-fold rise in HAI or a ≥ 4-fold rise in MN from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT). The proportion of participants who experience a post-vaccination antibody response at Week 16 (EOT) for HAI and the proportion of participants who experience a post-vaccination antibody response at Week 16 (EOT) for MN and corresponding 90% Clopper-Pearson exact CIs (Clopper et al 1934) will be summarized by treatment group.

The proportion of participants who achieve a post-vaccination HAI antibody titer ≥ 40 and the proportion of participants who achieve a post-vaccination MN antibody titer ≥ 40 at Week 16 (EOT) and corresponding 90% Clopper-Pearson exact CIs will be summarized by treatment group.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

The eight primary endpoints, as described in section 4.2.1.1, may be analyzed separately for the following, to show robustness around the specified intercurrent event strategies.

- Excluding participants who discontinue treatment
- Excluding participants who initiate any another medication, in line with IPDs listed in the PD specification.

4.2.2 Secondary Endpoint

4.2.2.1 Definition

The secondary objective is to assess the PK and immunogenicity, which will be done through serum trough tezepelumab concentrations and ADA. The analyses of the secondary endpoints will use the PK analysis set for the PK summaries and the safety analysis set for the ADA summaries.

4.2.2.2 Derivations

Due to the limited sampling schedule, the PK assessment will be based on the observed serum trough concentrations.

ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer).

For ADA and PK results reported as lower than the LLOQ, a value equal to half of the LLOQ will be imputed and used for analysis purposes.

4.2.2.3 Handling of Dropouts and Missing Data

If informed consent/assent to the study was withdrawn, all data up until the date of withdrawn informed consent/assent will be included.

4.2.2.4 Primary Analysis of Secondary Endpoint

4.2.2.4.1 Analysis of pharmacokinetics

The PK analyses will be performed by a third-party vendor under the guidance of AstraZeneca Research and Development.

Tezepelumab serum concentrations will be summarized using descriptive statistics at each visit. The following criteria will apply for data to be included in the summary table:

- Only samples collected prior to the first study intervention dose for baseline samples
- Only samples collected prior to influenza vaccination administration for pre-vaccination samples

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, geometric coefficient of variation (GCV), arithmetic mean and SD will be calculated by substituting the LLOQ divided by 2 for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, GCV, 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 GCV 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.

4.2.2.4.2 Analysis of immunogenicity

ADA to tezepelumab will be summarized using descriptive statistics at each visit by treatment group.

The ADA status across the study for each subject will also be classified and summarized 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 two 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 study intervention administration
- Subjects with treatment emergent ADA (ADA incidence): defined as the sum of treatment induced ADA and treatment boosted ADA.

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

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

Neutralizing ADA evaluations will be conducted on confirmed ADA positive samples. The test sample is deemed positive or negative for the presence of neutralizing antibodies (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/serious AEs (SAEs) may be evaluated.

CCI

[redacted]

CCI

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CCI

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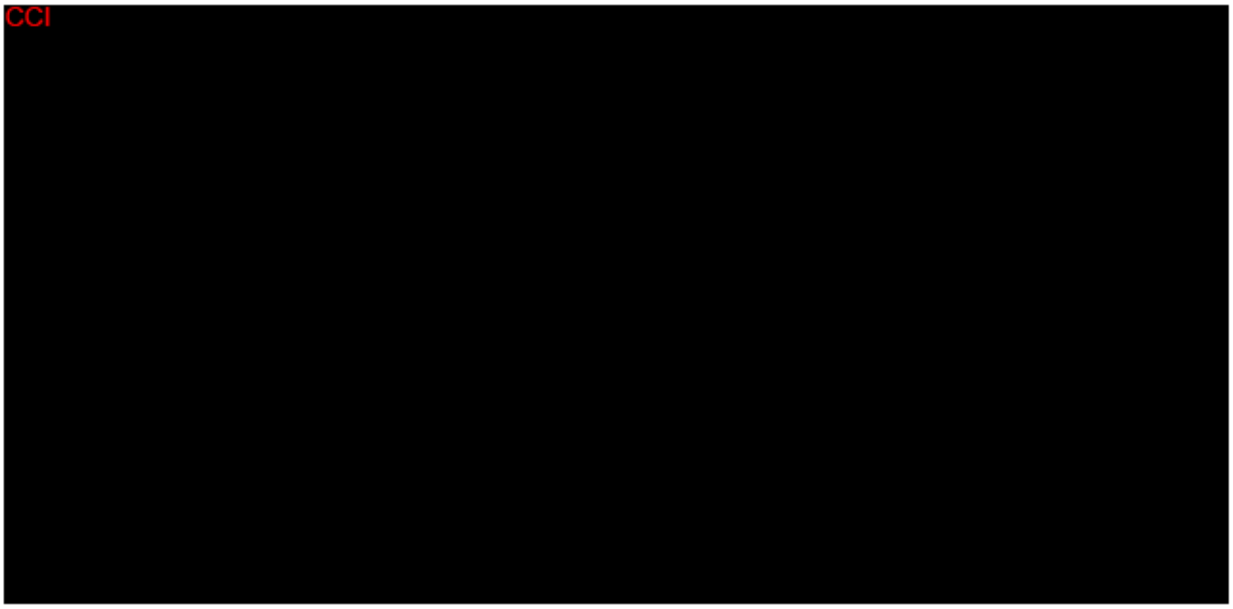

4.3 Pharmacodynamic Endpoint(s)

Refer to section 4.6.34.2.2 for details.

4.4 Pharmacokinetics

Refer to section 4.2.2 for details.

4.5 Immunogenicity

Refer to section 4.2.2 for details.

4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, and vital signs.

Tables are provided for the safety analysis set; listings are provided for all participants or the safety analysis set depending on the availability of data.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Duration of exposure to study intervention is defined as the number of days between the date of first dose and the date of last dose of study intervention inclusive, calculated as follows:

$$\begin{aligned} &Duration\ of\ exposure\ (days) \\ &\quad = minimum(date\ of\ last\ dose\ of\ \text{study intervention} \\ &\quad + 33\ days; date\ of\ death; date\ of\ study\ withdrawal) \\ &\quad - date\ of\ first\ dose\ of\ \text{study intervention}\ + 1 \end{aligned}$$

This calculation does not consider any gaps in exposure caused by the participant missing one or more intermediate scheduled weekly doses. Such cases will be identified in the CSR if they occur but will not explicitly be accounted for in any analysis. Date of last dose will include the unscheduled visits due to delayed flu vaccine administration, if applicable.

4.6.1.2 Presentation

Duration of exposure (days) will be summarized by treatment group and presented for the safety analysis set.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse Events (AEs) will be summarized for analysis according to their onset date into the following study periods:

- AEs occurring during screening: date of Visit 1 ≤ AE onset date < date of first dose of study intervention
- AEs occurring during on-treatment period: date of first dose of study intervention ≤ AE onset date ≤ minimum (date of last dose of study intervention +33 days, date of death, or date of study withdrawal)
- AEs occurring during on-study period: date of first dose of study intervention ≤ AE onset date ≤ study completion or date of study withdrawal.

Rules for imputing AE start/stop dates which are partially missing can be found in Appendix A: Partial Date Conventions for Adverse Events. Partially missing start/stop dates will appear as such in the participant data listings but will be imputed to permit proper tabulation of AE data.

AEs of special interest (AESIs) are an event of scientific and medical interest towards improving the understanding of the study intervention. An AESI may be serious or non-serious. Similar considerations apply to any additional supporting analysis of AESIs, in which MedDRA dictionary-based definitions are used. Derivation details (for those derived from the eCRF), or a statement when the derivation needs to be referenced externally to the SAP (for those derived from MedDRA dictionary terms), are given in Appendix 7.3.

4.6.2.2 Presentation

All AE summaries will be presented by actual treatment group for the safety analysis set. A by- participant listing of all AEs will be provided; AEs occurring during screening will be included in the listing, but not summarized separately. The number and percentage of participants with on-treatment and on-study AEs will be tabulated separately by system organ class and preferred term. An event that occurred one or more times during a period will contribute one observation to the numerator of the proportion. The denominator of the proportion will comprise all participants in the safety population. On-treatment AEs will also be summarized by intensity/severity and separately, by causality/relatedness (as determined by the investigator). Should a participant report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the participant's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to death, AEs leading to discontinuation from study intervention, and commonly occurring AEs (defined as those occurring in >5% of subjects in either treatment group) will be summarized by treatment group. AESIs will also be summarized descriptively by treatment group; serious infections will be summarized as part of the SAE by SOC and PT table in the SOC of infections and infestations and not in a separate table.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

A list of clinical chemistry and hematology variables can be found in the CSP. Baseline is defined as last available non-missing data collected prior to first dose of study intervention. Potential Hy's law definition and case confirmation are given in Appendix D of the CSP.

For results reported as lower than the LLOQ, a value equal to the LLOQ will be imputed and used for analysis purposes.

4.6.3.2 Presentations

Clinical chemistry and hematology data will be summarized by presenting shift tables and plots using normal ranges (baseline to minimum post-baseline value, baseline to maximum post-baseline value, and baseline to last observation on-study) and by presenting summary statistics of observed and change from baseline values (means, SDs, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarized.

In order to identify potential Hy's Law cases, maximum post-baseline total bilirubin (TBL) will be plotted separately against both maximum post-baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST), expressed as multiples of the upper limit of normal (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.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

A list of urinalysis variables can be found in the CSP. For results reported as lower than the LLOQ, a value equal to the LLOQ will be imputed and used for analysis purposes.

4.6.4.2 Presentations

Urinalysis data will be summarized by presenting shift tables (baseline to maximum post-baseline value, and baseline to last observation on-study).

4.6.5 Other Laboratory Evaluations

Not applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs collected include pulse rate, blood pressure, respiratory rate, and body temperature. Baseline is defined as last available non-missing data collected prior to the first dose of study intervention.

4.6.6.2 Presentations

Vital signs data will be summarized by presenting summary statistics of observed and change from baseline values by visit and treatment group. The frequency of changes (baseline to minimum post-baseline value, baseline to maximum post-baseline value, and baseline to last observation on-study) with respect to normal ranges (high/low/normal findings) will be tabulated and plotted by treatment group.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Twelve-lead electrocardiogram (ECG) measurements are performed locally and will be recorded in accordance with the CSP at visit 1 only. The outcome of the overall evaluation

is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

4.6.7.2 Presentations

All ECG measurements will be listed, along with the overall evaluation and significance of abnormality, if applicable.

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Any new physical exam finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE in AE reporting.

Any device malfunctions relating to an AE, will be reported as an AE.

4.6.8.2 Presentations

Physical exam findings and device malfunctions reported as an AE will be summarized as described in section 4.6.2. Any reported device malfunctions will be listed.

5 INTERIM ANALYSIS

There is neither an unblinded data review nor interim analysis planned for this study prior to primary database lock.

6 REFERENCES

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7 APPENDIX

7.1 Appendix A: Partial Date Conventions for Adverse Events

Missing type	Action
If only the **day part** of the AE **onset date** is missing the missing day of onset of 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 first study treatment • The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment • The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment.
If the **day and month parts** of the AE **onset date** are missing the date of onset of AE will be set to:	• January 1 of the year of onset, if the onset year is after the year of the first study treatment • The date of the first treatment, if the onset year is the same as the year of the first study treatment • The date of informed consent, if the onset year is before the year of the first treatment
If only the **day part** of the AE **resolution date** is missing the missing day of resolution of AE will be set to:	The last day of the month of the occurrence. If the participant died in the same month, then set the imputed date as the death date.
If the **day and month parts** of the AE **resolution date** are missing, the date of resolution of AE will be set to:	December 31 of the year of occurrence. If the participant died in the same year, then set the imputed date as the death date.

7.2 Appendix B: Imputation Rules for Missing/Partially Missing Prior/Concomitant Medication Dates

DATE MISSING	ACTION
Completely missing start date	Assume participant had been on the medication since the date of the first study procedure.
Partially missing start date (month/year or year only)	If the partially missing onset date is the same as that for the **end** of study intervention treatment, it will be assumed to have started on-treatment. If the partially missing onset date is the same as that for the **start** of IP treatment, it will be assumed to have started before treatment. If the partially missing onset date is prior to start of IP treatment, it will be assumed to have started January 1st if only year is present and assumed to have started the 1st day of the respective month if year and month are present.
Completely missing end date	Assume participant had been on the medication on the date of study completion or withdrawal.
Partially missing end date (month/year or year only)	If the partially missing end date is the same as that for the **start** of IP treatment, it will be assumed to have ended on-treatment. If the partially missing end date is the same as that for the **end** of IP treatment, it will be assumed to have ended post-treatment. If the partially missing end date is after the end of IP treatment, it will be assumed to have ended December 31st if only year is present and assumed to have ended the last day of the respective month if year and month are present.

7.3 Appendix C: Adverse events of special interest

AESIs and related definitions based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. These detailed definitions will be finalised by the study team prior to the primary database lock and provided together with the study datasets at the time of submission.

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.

Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

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.

Hypersensitivity reactions

Hypersensitivity reactions will be defined using a narrow SMQ excel file according to Integrated Summary of Safety (ISS) reporting.

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.

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".

Malignancy

Malignancy will be defined on the basis of an SMQ.

Opportunistic infections

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

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").

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