Statistical Analysis Plan	
Study Code	D5180C00011
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A Multicenter, Randomised, Open-label, Parallel-group, Functionality, and Performance Study of an Accessorized Pre-filled Syringe and Autoinjector with Home-administered Subcutaneous Tezepelumab in Adolescent and Adult Subjects with Severe Asthma (PATH-HOME)

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Explanation
ACQ-6	Asthma Control Questionnaire-6
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
AI	Autoinjector
ALT	Alanine Aminotransferase
APFS	Accessorized Pre-filled Syringe
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BD	Bronchodilator
BMI	Body Mass Index
CSR	Clinical Study Report
DAE	AEs Causing Discontinuation of Investigational Product
DBL	Data Base Lock
eCRF	Electronic Case Report Form
EOT	End of Treatment
FAS	Full Analysis Set
HCP	Health Care Professional
ICF	Informed Consent Form
ICS	Inhaled Corticosteroids
IFU	Instructions for Use
IP	Investigational Product
IPD	Investigational Product Discontinuation
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing Antibody
NHP	Non-Compliance Handling Plan
NQ	Non-quantifiable
PK	Pharmacokinetic(s)

Abbreviation or Special Term	Explanation
PT	Preferred Term
SAE	Serious Adverse Event
SAS	SAS Institute Inc., Cary, NC
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
WHO	World Health Organisation

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other: Section 2.1.3 Other analysis set	13JUL2020	Updated the definition of PK analysis set	No	To clarify that only patients with a detectable PK will be included in the analysis of PK concentrations
Derivation of primary or secondary endpoints: Section 2.1.4 Handling or other issues which may impact analysis set	13JUL2020	Added language to emphasize that worst outcome logic will apply to primary analysis only for subjects who had replaced devices	Yes	To clarify the application of this rule for secondary endpoints
Other: Section 2.2 Violations and derivations	13JUL2020	Added language for COVID-19 related PDs	Yes	To clarify the reporting of these PDs
Data presentation: Section 3.1.5 Visit windows	13JUL2020	Updated the Visit Window table	Yes	To accurately assign the visit window
Primary or secondary endpoints: Section 3.2.1 Primary endpoints	13JUL2020	Added assessment “Week 0” for the summary of HCPs	Yes	To include all visits in the summary table
Primary or secondary endpoints: Section 3.2.2 Secondary endpoint	13JUL2020	Added “Only returned and evaluated devices will be counted towards secondary endpoints.”	Yes	To clarify the application of this rule for secondary endpoints
Statistical analysis method for secondary endpoint: Section 3.2.3 Asthma Control Questionnaire (ACQ6)	13JUL2020	1. Updated “Week 20” to “Week 24 2.Updated the rule for deterioration to “>= 0.5”	Yes	Typo
Other:	13JUL2020	1.Added the definition of “on-study””	Yes	To clarify the reporting

Section 3.3.2 Adverse events		2. Replaced text "treatment emergent" to "on-treatment"		periods
Other: Section 3.3.4 Laboratory variables	13JUL2020	Updated "ULOQ/2" to "ULOQ"	Yes	In line with new AZ guideline on reporting safety data.
Other: Section 4.2.1 Subject disposition, demography and baseline characteristics	13JUL2020	Added language for the analysis of COVID-19 related PDs	Yes	To clarify summarisation of these PDs
Other: Section 4.2.2 Prior and concomitant medications	13JUL2020	Updated "Safety analysis set" to "FAS"	Yes	To be consistent with other tezepelumab studies
Statistical analysis method for the primary or secondary endpoints: Section 4.2.4.1 Primary analyses	13JUL2020	Added language for sensitivity analysis	Yes	To clarify how to handle devices that were not evaluated in the analysis
Statistical analysis method for the primary or secondary endpoints: Section 4.2.5 Secondary outcome variables	13JUL2020	1. Added language for summary of Product Complaints by malfunctioning reason 2. Added language to specify selection rule for multiple attempts of administration due to failure	Yes	1. To clarify reporting of product complaints 2.To clarify how to handle devices that were not evaluated and multiple attempts in the analysis
Other: Section 4.2.6.1 Adverse events	13JUL2020	1. Updated "post-treatment" to "on-study" 2. Updated the summary of AEs by causality and maximum intensity by PT only 3. Added text to clarify summary of AEs related to device malfunction	Yes	To clarify the reporting periods be consistent with other tezepelumab studies.
Other: Section 4.2.6.2 Laboratory data	13JUL2020	1. Added "during on-study period" for the summary of the lab data 2. Updated to summarize the shift tables for	Yes	To clarify reporting period and to and be consistent with other tezepelumab

		baseline and maximum/minimum/last, post-baseline values for each variable. 3. Added "Both shift tables and shift plots will be produced using all data for the on-study period." 4. Added "The urine microbiology data will be listed only."		studies
Other: Section 4.2.6.3 Vital signs	13JUL2020	1 Updated "on-treatment" to "on-study" 2. Removed "missing" category from shift tables	Yes	To summarize all data collected and to be consistent with other tezepelumab studies
Other: Section 4.2.7.2 Analysis of immunogenicity	13JUL2020	Updated the section (study ADA categories)	Yes	In line with new AZ guideline on reporting immunogenicity data.
Other: Section 6 Change of analysis from protocol	13JUL2020	Added changes from protocol of 1. PK analysis set definition 2. Cut-off value of well-controlled category of ACQ-6	N/A	To document these changes from analysis from protocol
Other: Appendix 8.1.1 Adverse events of special interest	13JUL2020	Removed Immune complex disease from Section 8.1.1 and made it a new separate section.	Yes	To be consistent with other tezepelumab studies
Whole document	03SEP2020	Formatting and links fixed	N/A	No changes to content, however formatting reflecting house style and errors in links resolved

*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
N/A = Not applicable

1. STUDY DETAILS

This is the statistical analysis plan (SAP) for study D5180C00011. The SAP describes the statistical analyses specified in the latest version of the clinical study protocol (CSP) in more detail; any changes to what is specified in the CSP will be described in Section 6.

1.1 Study objectives

1.1.1 Primary objective

Primary objective:	Endpoint/variable:
To assess the successful administration of tezepelumab 210 mg subcutaneous (SC) by injection with an Accessorized Pre-filled Syringe (APFS) or Autoinjector (AI) device in clinic and at home	• Proportion of Health Care Professionals (HCPs) and subjects/caregivers who successfully administrated tezepelumab in clinic and at home with an APFS • Proportion of HCPs and subjects/caregivers who successfully administrated tezepelumab in clinic and at home with an AI

1.1.2 Secondary objectives

Secondary objective:	Endpoint/variable:
To assess the functionality of the APFS or AI devices utilised to administer tezepelumab in clinic and at home	• Proportion of used/returned APFS devices that passed functional tests and visual inspection and showed no evidence of malfunction • Proportion of used/returned AI devices that passed functional tests and visual inspection and showed no evidence of malfunction
To assess the performance of APFS or AI devices used to administer tezepelumab in clinic and at home	• Proportion of APFS devices that have been reported as malfunctioning (Product Complaints) • Proportion of AI devices that have been reported as malfunctioning (Product Complaints)

Secondary objective:	Endpoint/variable:
To monitor the metrics of asthma control	• Change from baseline in Asthma Control Questionnaire-6 (ACQ-6) score
To assess the pharmacokinetics and immunogenicity of tezepelumab administered via APFS or AI in clinic and at home	• Serum trough concentrations Anti-drug antibodies (ADA)

1.1.3 Safety objective

Safety objective:	Endpoint/variable:
To assess the safety and tolerability of tezepelumab	• Adverse events/serious adverse events • Laboratory parameters

1.2 Study design

This is a Phase 3, multicentre, randomised, open-label, parallel-group study designed to assess the performance of a single-use APFS and AI with a fixed 210 mg dose of tezepelumab administered SC in the clinic and an at-home setting.

The study will consist of a screening/run-in period up to 2 weeks, a treatment period of 24 weeks and a post-treatment follow-up period of 12 weeks. During the treatment period, one dose level of tezepelumab 210 mg will be administered SC via a single-use APFS or AI every 4 weeks (Q4W) starting at Week 0 until Week 20. Investigational product (IP) will not be administered at Week 24.

Approximately 210 subjects with severe asthma will enter the treatment period to receive 6 SC doses (Week 0, Week 4, Week 8, Week 12, Week 16, and Week 20) of tezepelumab. The first 3 doses of tezepelumab will be administered in the clinic, the next 2 doses will be administered at home, and the last dose at the clinic. Approximately 20 adolescents aged 12 to 17 years will be included. Subjects will be randomised globally in a 1:1 ratio to the following groups:

- Tezepelumab 210 mg to be administered SC via APFS
- Tezepelumab 210 mg to be administered SC via AI

All subjects will be stratified at randomisation by age (adults (18-80 years)/adolescents (12-17 years)) and by country.

As part of the informed consenting process, the APFS and AI Instructions For Use (IFU) and administration questionnaire will be reviewed by the subjects/caregivers. Following a 2-week screening period, eligible subjects will receive 4 SC doses of tezepelumab 210 mg at the clinic (Week 0, Week 4, Week 8, and Week 20) and 2 SC doses of tezepelumab 210 mg at home (Week 12 and Week 16). At Week 0, the HCP will administer the study drug. At Week 4, the

subject or caregiver will have the option of administering the study drug under HCP supervision to ensure they understand the procedure and are capable of doing so. At Week 8, the subject or caregiver will have to perform the injection, again under HCP supervision. Subjects or subjects with caregivers who are unable or unwilling to administer IP at Week 8 (Visit 4) will be discontinued from the study.

At Week 12 and Week 16, tezepelumab will be self-administered by the subject or administered by the caregiver at home on weekdays when the physician office or clinic is open. The subject or caregiver will be given the IFU as a reference for home administrations. After each of these administrations, the subject will return for a scheduled on-site visit within 48 hours. For adolescent subjects who will self-administer the IP, the caregiver or an adult must supervise IP administration.

The final dose of tezepelumab (Week 20) will be self-administered by the subject or administered by the caregiver at the clinic under HCP supervision in order to evaluate administration technique.

When IP is administered in the clinic at Week 0, Week 4, Week 8, and Week 20, the person administering the dose will fill out an administration questionnaire designed to indicate if the dose was successfully administered or not. The site is to subsequently return the used devices and completed questionnaires to the Sponsor for evaluation.

When IP is administered at home (Week 12 and Week 16), whether the subject is self-administering, or the caregiver is administering to the subject, the person administering the dose will fill out an administration questionnaire designed to indicate whether the dose was successfully administered or not. Both the completed questionnaire and the used device are to be returned to the site during each of the on-site visits scheduled within 48 hours of the home administration of IP (Week 12 and Week 16). The site is to subsequently return the used devices and completed questionnaires to the Sponsor for evaluation.

The same person must administer the IP at Weeks 4 (if administered by subject/caregiver), 8, 12, 16, and 20, whether it is the subject or caregiver.

1.3 Number of subjects

Approximately 210 subjects will be randomised, out of which 105 will receive a dose of tezepelumab 210 mg via APFS injection and 105 will receive the same dose administered via AI. Approximately 20 adolescents aged 12 to 17 years will be included. It is anticipated that approximately 5% of subjects will drop out and thus it is estimated that approximately 100 subjects will complete the study for each device.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Enroled subjects:

This comprises all subjects who signed an informed consent form (ICF), including screen failures, and will be used for disposition reporting.

2.1.1 Efficacy analysis Set

Full analysis set (FAS)

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

Analyses associated with successful use of devices will be performed using FAS and subjects will be analysed according to their randomisation group (including in the case of any discrepancies between randomised and actual device type). Details are described in the following analysis sections. Demographics and baseline characteristics will be summarised using this analysis set as well.

2.1.2 Safety analysis set

Safety analysis set

This comprises all subjects who received at least one dose of tezepelumab.

Safety analyses will be performed using all subjects in the safety analysis set. Subjects will be analysed according to their actual device type used initially in the case of any discrepancies between randomised and actual device type.

Safety data will also be listed separately for any subject who administered IP by a device at one or more visits which was not in the device type as randomised.

Summaries of ADA will also be based on the safety analysis set.

2.1.3 Other analysis set

PK analysis set

This analysis set comprises all subjects in the full analysis set who received tezepelumab treatment and had at least one detectable serum concentration from a sample collected post-treatment that is assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received).

All PK summaries will be based on this analysis set.

2.1.4 Handling of other issues which may impact analysis sets

If it is found that any subject has been randomised on more than one occasion (contrary to the protocol) under different subject numbers, either at the same site or at different sites, then the

first subject occurrence will be included in the relevant analysis sets defined above, and only data associated with that first subject occurrence will be used in analyses. Data associated with the second (and any subsequent) occurrences of the same subject will be listed and discussed in the CSR but will not be included in the summaries. All data associated with duplicate randomisations will be reviewed, and decisions regarding the analysis and reporting of these data will be documented, prior to Database Lock (DBL).

If it is found that any subject has used more than one device for the same visit administration due to device malfunction, then the attempt with the worst outcome will be included in the analyses related to this visit for primary analysis only (i.e., in calculation of the proportion of HCPs and subjects/caregivers who successfully administrated tezepelumab in clinic or at home with an APFS or AI). In the analyses related to device functionality or product complaints, multiple devices that were used/returned are included in the analyses. The above analysis set definitions assume the integrity of data captured from all participating sites in the trial. If it is deemed necessary to exclude subjects from analysis sets due to suspected fraud/other serious non-compliance at a particular site, or to perform sensitivity analyses with subjects from such a site removed for the same reason, this will be documented in this SAP (amended if necessary) when possible prior to DBL. Otherwise, it will be fully described in the CSR. After DBL the SAP will not be updated.

2.1.5 Definition of on-treatment

The period from the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal) will be considered as on-treatment. This allows inclusion of any information which may be reported at or generated from the IP Discontinuation (IPD) visit to be considered as on-treatment, provided the IPD visit is within the protocol visit window after premature discontinuation of IP.

2.2 Violations and deviations

Important PDs and COVID-19 related PDs (including important and non-important PDs) will be listed and tabulated in the CSR and only for randomised subjects (i.e. not screening failures). Important PDs 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. They may include (but not be limited to):

- Subjects who were randomised even though they did not meet key entry criteria
- Subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who had IP administered with the wrong device type
- Subjects who received an excluded concomitant treatment

All PDs will be identified and documented by the study team prior to DBL. As much as possible, the occurrence of PDs will be monitored during the trial with the emphasis on their future prevention.

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

The study Non-Compliance Handling Plan (NHP) outlines the management of PDs and includes the proposed categories of PDs in this trial.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Age calculation

Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. For subjects in countries where date of birth is not recorded, the age as recorded in the eCRF will be used.

3.1.2 Definition of baseline

In general, the last non-missing measurement prior to first dose of study treatment will serve as the baseline measurement, unless otherwise specified. If there is no value prior to first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

Where unscheduled/repeat assessments are relevant and exist for any subject at a particular visit specified below, they will also be considered in the baseline definitions, provided they remain prior to the date of first dose of study treatment. Visit 2 (Week 0) is the planned baseline visit per study design.

For assessment without time collected (with exception of adverse events), the assessment on the same day of the first dose will be assumed to be a pre-dose assessment.

3.1.3 Absolute change from baseline

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

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

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

3.1.4 Study periods

The following study periods are defined for analysis purposes:

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

- Planned treatment period (on-treatment and off-treatment): starting on the date of first dose of IP and ending on the date of the Week 24 visit or earlier study withdrawal date.

- On-treatment period: starting and ending on the start and end dates defined in Section 2.1.5.

- Post-treatment period: starting one day after the end date defined in Section 2.1.5, respectively, and ending on the study completion or withdrawal date.

- On-study period (planned treatment and follow-up): starting on the date of first dose of IP and ending on the study completion or withdrawal date.

3.1.5 Visit windows

All summaries and analyses which are presented by time point (e.g. "Week 24") will use a visit window to classify the data record with the exception of PK/ADA data which will be analysed by using the nominal visits. The visit window is derived from the assessment date relative to the reference start date. This approach allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing (notably the IPD visit), and the handling of data captured at visits for which the database label is incorrect and unresolvable.

For relative day calculation, the reference start date is the date of first dose of IP and relative day is therefore defined as the *(Date of assessment – Date of first dose of IP)* for pre-dose assessment and the *(Date of assessment – Date of first dose of IP) + 1* for post-dose assessment.

Any data collected at unscheduled or repeat visits will be listed. These data will be included in baseline definitions (see Section 3.1.2) and in any definitions of maximum value, minimum value or last value within the relevant study period.

Data collected at unscheduled or repeat visits will also be included in visit windows, and therefore may be included in summaries or analyses by visit. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled or repeat assessment within the same visit window, the non-missing value at the unscheduled/repeat assessment will replace the missing value at the scheduled visit.

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

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

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

The same visit window definitions below will be used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.1.4). In practice, each data record in the planned treatment period will be first identified, and then further flagged according to whether it is on-treatment or off-treatment. This flag will be used to select all eligible records for subsequent visit windowing, according to whether the derived visits are to be used in a planned treatment period or an on-treatment period analysis. It should be noted that, if treatment was discontinued within a particular visit window, the rules above for handling multiple values within the same visit window could select a different record according to whether a planned treatment period analysis or an on-treatment period analysis is needed.

In planned treatment period analyses any off-treatment assessments measured at a follow-up visit (scheduled 10 weeks after last IP administration), which occurred earlier than scheduled follow-up visits Week 30, or Week 36, will be considered in an earlier planned treatment period visit window, where applicable.

The following table summarizes the visit windows to be used. “Visit Window 1” corresponds to the full (mostly 4-weekly) protocol scheduling and will be used for all variables by default, including those variables which are not captured according to the full protocol schedule, and for which only certain weeks displayed in “Visit Window 1” therefore apply. An assessment will be made during review of the extent to which values for variables which do not follow the complete protocol schedule are falling outside the windows for the relevant weeks using “Visit Window 1”. Following the review, a decision may be made to apply one of the alternative visit window rules displayed below to any such variables.

Table 1 Visit windows

Time point	Target day	Visit Window 1 (Efficacy endpoints, Vital signs)	Visit Window 2 (Lab)
Baseline (Week 0)	1	See Section 3.1.2 for baseline definitions	
Week 4	29	2-42	x
Week 8	57	43-70	x
Week 12	85	71-98	x
Week 16	113	99-126	x
Week 20	141	≥127[1], 127-154[2]	x
Week 24	169	155-189	2-210
Follow-up Week 30	211	190-231	x
Follow-up Week 36	253	232-266	211-266

[1] Used for efficacy endpoints which include questionnaire information, collected up to Week 20.
[2] Used for vital signs and ACQ-6.

3.1.6 Prior and concomitant medication

Medications taken by any subject at any time during the study will be coded using the Anatomical Therapeutic Chemical (ATC) classification system within the World Health Organisation (WHO) Drug Dictionary.

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

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

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

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

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

3.2 Derivation of efficacy variables

3.2.1 Primary endpoints

To assess successful administration of the tezepelumab 210 mg injection via APFS and AI both in clinic and at home, the following outcomes will be measured for APFS and AI devices separately:

Primary Endpoint	**Analysed by**
Proportions of HCPs and subjects/caregivers who successfully administered tezepelumab in clinic or at home	• Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Combined (all weeks)
Additional presentations to primary endpoint	
Proportions of HCPs who successfully administered tezepelumab in clinic	• Week 0 (by HCP) • Week 4 (by HCP)
Proportions of subjects/caregivers who successfully administered tezepelumab in clinic or at home	• Week 4 (by subjects/caregivers) • Combined subjects/caregivers (Weeks 8, 12, 16, and 20)
Proportions of subjects/caregivers who successfully administered tezepelumab at home	• Combined at-home administration visits (Weeks 12 and 16)
Proportions of subjects/caregivers who successfully administered tezepelumab at clinic	• Combined at-clinic administration visits (Weeks 8 and 20)

In addition to the above presentation, a summary by subjects, separately by caregivers will be provided at individual Weeks: 4, 8, 12, 16, and 20; combined for Weeks 8, 12, 16, and 20; combined at-home administration visits (Weeks 12 and 16); combined at-clinic administration visits (Weeks 8 and 20), for each device type.

The proportions will be calculated among all subjects who received or attempted to receive an administration at specified visit. For combined presentations, the denominator will be the

number of subjects who received or attempted to receive an administration at all specific visits. A successful administration is defined as an injection completed based on a user-recorded answer of "Yes" to all 5 questions in the APFS/AI Questionnaire and a satisfactory in vitro evaluation (visual + functional evaluation) of the returned devices.

3.2.2 Secondary endpoints

To assess successful functionality and performance of the tezepelumab 210 mg injection via APFS and AI both in clinic and at home, the following outcomes will be measured as secondary endpoints of this analysis, for APFS and AI devices separately:

Secondary Endpoints	**Analysed by**
Proportions of used/returned devices that pass functional tests and visual inspection and showed no evidence of malfunction	• Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Combined (all weeks)
Proportions of devices that have been reported as malfunctioning (Product Complaints)	• Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Combined (all weeks)
Additional presentation to secondary endpoints	
Proportions of used/returned devices administered by HCP that pass functional tests and visual inspection and showed no evidence of malfunction	• Week 4 (by HCP) • Combined (Week 0 and Week 4 by HCP)
Proportions of used/returned devices administered by subjects/caregivers that pass functional tests and visual inspection and showed no evidence of malfunction	• Week 4 (by subjects/caregivers) • Combined (Weeks 4 by subjects/caregivers, 8, 12, 16, and 20)
Proportions of used/returned devices administered at home that pass functional tests and visual inspection and showed no evidence of malfunction	• Combined at-home administration visits (Weeks 12 and 16)
Proportions of used/returned devices administered in clinic by subjects/caregivers that pass functional tests and visual inspection and showed no evidence of malfunction	• Combined in-clinic administration visits (Weeks 8 and 20)
Proportions of devices administered by HCPs that have been reported as malfunctioning (Product Complaints)	• Week 4 (by HCP) • Combined (Week 0 and Week 4 by HCP)
Proportions of devices administered by subjects/caregivers that have been reported as	• Week 4 (by subjects/caregivers) • Combined (Weeks 4 by

malfunctioning (Product Complaints)	subjects/caregivers, 8, 12, 16, and 20)
Proportions of devices administered at home that have been reported as malfunctioning (Product Complaints)	• Combined at-home administration visits (Weeks 12 and 16)
Proportions of devices administered in clinic administered by subjects/caregivers that have been reported as malfunctioning (Product Complaints)	• Combined in-clinic administration visits (Weeks 8 and 20)

In addition to the above presentations, a summary by subjects, separately by caregivers will be provided at individual Weeks: 4, 8, 12, 16, and 20; combined for Weeks 8, 12, 16, and 20; combined at-home administration visits (Weeks 12 and 16); combined at-clinic administration visits (Weeks 8 and 20), for each device type, and for above two endpoints separately.

These proportions will be calculated by using the number of used and returned devices as denominator at specified visit. For the combined presentations, the denominator will be the cumulative number of used and returned devices over relevant visits.

The visual inspection will assess the returned devices for any visible damage or disassembly, full plunger travel indicating a complete dose was expelled, and needle guard deployment. The functional evaluation will challenge the needle safety guard to assess whether it deployed correctly and continued to provide protection against accidental needle stick injuries. Any device defects reported during the in vitro evaluation will result in a full product complaint investigation.

In the event that the answers to one or more of the questions on the questionnaire indicate that the user was unable to complete a successful administration, an evaluation will be performed on the returned device. The evaluation will take into account information provided on the administration questionnaire. If the in vitro evaluation of the device shows no observable device defect, then the unsuccessful administration may be classified as a use error and not a device malfunction. Only returned and evaluated devices will be counted towards secondary endpoints.

3.2.3 Asthma Control Questionnaire (ACQ-6)

Subject reported outcomes using ACQ-6 will be performed at the study site with paper questionnaires. Subjects will be given a paper questionnaire and be asked to complete and return these at Weeks -2, 0, 4, 8, 12, 16, 20, 24 and IPD.

The ACQ-6 captures asthma symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, wheezing) and short-acting β2-agonist use. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The

ACQ-6 score is computed as the unweighted mean of the responses to the 6 questions. If response to any of the questions is missing, the ACQ-6 score will be missing.

The outcome variable for ACQ-6 will be the change in mean score from baseline to each of the post-dose visits. There will be no imputation for missing values.

Asthma control responder status will be evaluated as a supportive analysis. Subjects will be categorized according to the following limits (Juniper et al. 2005), at the end of treatment, where end of treatment is defined as Week 24 (EOT visit):

1. ACQ-6 responder (Yes=1/No=0):
    - Responder: ACQ-6 (EOT - baseline) score ≤ -0.5
    - Non-responder: ACQ-6 (EOT - baseline) score > -0.5
2. ACQ-6 response (Improved/No change/Deterioration):
    - Improvement: ACQ-6 (EOT - baseline) score ≤ -0.5
    - No change: -0.5<ACQ-6 (EOT - baseline) score < 0.5
    - Deterioration: ACQ-6 (EOT - baseline) score >= 0.5

Subjects with missing or non-evaluable ACQ-6 data at end of treatment visit will be considered non-responders.

Additionally, subjects will be categorised according to their ACQ-6 defined asthma control status at EOT using the following score thresholds (Juniper et al. 2006):

- Well controlled: ACQ-6 (EOT) ≤ 0.75
- Partly controlled: 0.75 < ACQ-6 (EOT) < 1.5
- Not well controlled: ACQ-6 (EOT) ≥ 1.5

3.3 Derivation of safety variables

3.3.1 Exposure to IP and treatment compliance

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

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

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

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

Treatment compliance will be calculated as follows:

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

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

3.3.2 Adverse events (AEs) - general

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

AEs will be separated according to their onset date into the following study periods:

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

AEs occurring during screening run-in period will be listed only.

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

3.3.3 Adverse events of special interest

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

Similar considerations apply to any additional supporting analysis of AESIs, in which MedDRA dictionary-based definitions are used.

3.3.4 Laboratory variables

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times detailed in the protocol, and will be assessed in a central laboratory. Urine samples will be analysed locally and sent for analysis at the central laboratory only if a positive dipstick result for any parameter is observed.

The parameters outlined in Section 8.2.1, Table 6 of the CSP will be collected. Changes from baseline in continuous laboratory variables will be calculated at relevant visits as specified in Section 3.1.2 and Section 3.1.3.

In summaries, figures, and listings lab results and normal ranges will be presented in System International (SI) units.

In all analysis of continuous laboratory variables, any value recorded only as below Lower Limit of Quantification (LLOQ) will be set to LLOQ and included in the analysis. Any value recorded only as above Upper Limit of Quantification (ULOQ) will be set to ULOQ and will be included in the analysis. 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 ranges will be used for laboratory variables. All values falling outside the reference ranges will be flagged. These classifications will also be used for shift tables.

For the purposes of shift tables, baseline will be defined as specified in Section 3.1.2. The last values will be calculated across all visits in the relevant study period will use all available values including those from unscheduled and repeat visits, and irrespective of whether the values have been selected for use in summaries using visit windows (see Section 3.1.5).

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

- Aspartate aminotransferase (AST) $\geq$ 3 x ULN
- Alanine aminotransferase (ALT) $\geq$ 3 x ULN
- Total bilirubin (TBL) $\geq$ 2 x ULN

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

3.3.5 Vital signs

Changes from baseline in vital signs variables (pulse rate, systolic blood pressure (BP), diastolic BP, respiratory rate, body temperature, body weight/height, BMI) will be calculated at relevant clinic visits as specified in Section 3.1.2 and Section 3.1.3.

BMI is calculated as:

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

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

Table 2 Vital signs reference ranges				
Parameter	**Standard Units**	**Lower Limit**	**Upper Limit**	**Change from Baseline Criteria**
Diastolic Blood Pressure (sitting)	mmHg	60	100	±15
Systolic Blood Pressure (sitting)	mmHg	90	160	±30
Pulse Rate (sitting)	Beats/min	50	100	±20
Respiratory Rate	Breaths/min	8	20	
Body Temperature	Celsius	36.0	37.5	
Weight	kg	40	150	

3.4 Pharmacokinetic and immunogenicity

3.4.1 Pharmacokinetic variables

Serum samples for determination of tezepelumab concentrations and are collected on dosing visits (Week 0, Week 4, Week 20) prior to dosing, Week 24 (EOT) or IPD visit, and Week 36 follow-up visit.

Samples for determination of tezepelumab concentration in serum will be analysed by a designated third party on behalf of AstraZeneca using a validated bioanalytical method.

3.4.2 Immunogenicity variables

Immunogenicity assessments will be collected from all subjects at Week 0, Week 4, Week 24 (EOT) or IPD visit, and at Week 36 follow-up visit. Samples collected on dosing visits (Week 0, and Week 4) are prior to dosing.

Samples will be measured for the presence of ADAs for tezepelumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titre assay components, and positive-negative cut points statistically determined from drug-naïve samples will be employed.

Samples confirmed positive for ADA will be archived for possible testing for neutralizing antibodies (nAb).

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Statistical hypotheses for primary efficacy variables

No statistical hypotheses will be tested in this study.

4.2 Analysis methods

4.2.1 Subject disposition, demography and baseline characteristics

Subject disposition will be summarised using enroled subjects. The number of enroled subjects and not randomised (and reason) will be summarised. The number and percentage of subjects within each device type will be presented by the following categories: randomised, received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and discontinued study (including reason).

The number of subjects randomised by country and center will also be summarised in the FAS by device type.

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

Demographic data such as age, sex, race, and ethnicity will be summarised for the all subjects in the FAS by device type.

Various baseline characteristics will also be summarised in the FAS by device type, which include respiratory disease history, weight, height and BMI, smoking status, history of allergy, baseline lung function, asthma duration, age at onset of asthma, asthma medications, and exacerbation during previous 12 months.

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

Important PDs will be summarised by device type for the FAS. COVID-19 related PDs (important and non-important) will be listed for subjects in FAS.

4.2.2 Prior and concomitant medications

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented in the FAS by device type. Separate tables will be presented for all medications received during each of the following periods as defined in Section 0: Prior, Concomitant (on-treatment), Concomitant (post-treatment).

Tables for maintenance medications (started prior to and ongoing after the first day of IP) will be produced displaying the baseline total daily dose of Inhaled Corticosteroids (ICS) medications. The number of subjects using other maintenance asthma medications at baseline will also be summarised.

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

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

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

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

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

4.2.3 Exposure and compliance

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

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

In addition, duration of study periods (as defined in Section 3.1.4) will be summarized by device types.

4.2.4 Primary outcome variables

4.2.4.1 Primary analyses

For the primary endpoint and each of the presentations of the primary endpoint detailed in Section 3.2.1, proportions and their corresponding exact 95% confidence intervals (CIs) using Score CI (Agresti et al. 1998) method will be presented in the FAS by device types.

The same analysis will be repeated for the adult/adolescent subjects.

In case of used devices that are not returned or not evaluated by the in-vitro evaluation team, sensitivity analysis will be performed by excluding these devices from the denominators on the primary endpoint. In case of multiple attempts of administration due to failure of the first attempt, the result of the worst attempt - unsuccessful administration will be counted in the analysis.

4.2.5 Secondary outcome variables

The secondary outcome variables and each of the presentations of the secondary endpoints in Section 3.2.2 will be analysed using similar methods as for the primary outcome variables.

The same analysis will be repeated by age group for the device functionality related endpoints.

A summary of proportions (n, %) of devices that have been reported as malfunctioning (Product Complaints) by malfunctioning reason and visit will also be provided for each device type. These proportions will be calculated by using the number of used and returned devices as denominator at specified visit.

Used devices that are not returned or not evaluated will not be included in the secondary endpoint analyses. In case of multiple attempts of administration due to failure of the first attempt, the results of every attempt will be counted in the analyses.

4.2.5.1 ACQ-6 score

Descriptive summary statistics (n, mean, SD, median, minimum and maximum) of ACQ-6 score will be presented for the absolute value and the change from baseline at each visit in FAS by device type.

The number and percentage of ACQ-6 responders (yes, no), and subject's asthma control status (well controlled, partially controlled, and not well controlled) at both baseline and Week 24 will be summarised in the FAS by device type.

Additionally, the number and percentage of subjects achieving an improvement, no change, or deterioration, as per Section 3.2.3, will be summarised.

4.2.6 Safety outcome variables

All safety variables will be summarised using the safety analysis set.

4.2.6.1 Adverse events

Adverse events will be summarised for the on-treatment, and on-study periods as defined in Section 3.1.4. All AE summaries will be presented by device type and total. All AEs will be listed regardless of treatment period.

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 leading to death, AEs leading to discontinuation from IP (DAEs), and adverse events of special interest (AESIs). The total number of AEs in the different AE categories will also be presented as well as the number of subjects (i.e. accounting for multiple occurrences of the same event in a subject) by device type.

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

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

- SAEs
- AEs leading to death
- DAEs
- AEs leading to discontinuation of IP
- The most common AEs (defined as those occurring in >3% of subjects in either device type) by PT only

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

AEs related to device malfunction will be listed by device type.

AEs of Special Interest (AESIs) will also be summarised descriptively by device type.

Separate listings of subjects with AEs, SAEs, AEs leading to death, AEs leading to discontinuation of IP will be presented.

4.2.6.2 Laboratory data

All continuous laboratory variables will be summarised by absolute value at each visit by device type, together with the corresponding changes from baseline. These summaries will be produced for all visits, during on-study period. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and standard deviation (SD). Mean changes from baseline over time will also be plotted by device type.

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

Both shift tables and shift plots will be produced using all data for the on-study period.

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

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

For all subjects who meet the biochemical criteria for Hy's Law (potential Hy's Law cases), the relevant laboratory variables will be tabulated showing all visits for these subjects.

Subjects with elevated ALT or AST in addition to elevated TBL at any time may be explored further graphically using individual subject profile plots.

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

The urine microbiology data will be listed only.

4.2.6.3 Vital signs

All vital signs variables will be summarised by absolute value at each visit by device type, together with the corresponding changes from baseline. These summaries will be produced for the on-study period. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

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

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

Both shift tables and shift plots will be produced using all data for the on-study period.

Number and percentage of subjects who have changes from baseline outside the pre-defined AZ clinically important change criteria in Section 3.3.5 will be presented. All data for the on-study period will be used.

4.2.7 Pharmacokinetics and immunogenicity

4.2.7.1 Analysis of pharmacokinetics

PK variables will be summarised using pharmacokinetics analysis set.

Tezepelumab serum concentrations will be summarised presented by visit for each device separately by using descriptive statistics. For descriptive statistics of tezepelumab concentrations:

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

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

Observed serum concentrations of tezepelumab for each individual will be listed by visit to confirm tezepelumab administration.

4.2.7.2 Analysis of immunogenicity

All analyses of immunogenicity variables will be based on the safety analysis set.

The number and percentage of ADA-positive subjects at each visit will be summarised by device type. Descriptive statistics of ADA titres (minimum, Q1, median, Q3, and maximum) will be provided by device type at each visit.

The ADA status -during the study for each subject will also be classified and summarised by device type. Specifically, the following ADA results will be evaluated as number and proportion of subjects together with corresponding titre summaries.

- Subjects who are ADA positive at baseline and/or post-baseline (ADA prevalence).
- Subjects who are ADA positive at baseline
- Subjects who are ADA positive at baseline only.
- Subjects who are ADA positive post-baseline.
- Subjects who are both ADA positive at baseline and positive in at least one post-baseline assessments.
- Subjects who are treatment-induced ADA positive, defined as ADA negative at baseline and post-baseline 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, defined as either treatment induced ADA positive or treatment-boosted ADA positive.
- Subjects who are ADA persistently positive, defined as ADA positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or ADA positive at the last post-baseline assessment.
- Subjects who are ADA transiently positive, defined as having at least one post-baseline ADA positive assessment and not fulfilling the conditions of ADA persistently positive.

Association of ADA with pharmacokinetics of tezepelumab and safety may be analysed, if appropriate.

5. INTERIM ANALYSES

No interim analysis is planned in this trial.

6. CHANGE OF ANALYSIS FROM PROTOCOL

The protocol specifies subjects as not well-controlled when unweighted mean in ACQ-6 asthma is >1.5. The SAP states that not well controlled subjects should be defined when the mean is ≥1.5 as per the reference from Juniper et al. 2006.

The protocol defines the PK analysis set as "All subjects in the full analysis set who received tezepelumab and from whom PK blood samples are assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received)." However, its definition in the SAP has been update to "All subjects in the full analysis set who received tezepelumab treatment and had at least one detectable serum concentration from a sample collected post-treatment that is assumed not to be affected by factors such as protocol deviations (e.g. disallowed medication or incorrect study medication received)." to help with the interpretation of PK summary analysis.

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8. APPENDIX

8.1 Adverse events of special interest

8.1.1 Anaphylactic reactions

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

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

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

8.1.2 Immune complex disease (Type III hypersensitivity reaction)

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

8.1.3 Malignancy

Malignancy will be defined on the basis of an SMQ.

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

8.1.4 Helminth infections

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

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

8.1.5 Severe infections (as defined in the protocol)

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

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

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

- AE resulted in permanent discontinuation of study drug ("Action taken, investigational product" on Adverse Events eCRF page marked as "Drug permanently discontinued").

8.1.6 Injection site reactions

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

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

8.1.7 Opportunistic infections

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

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

8.1.8 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

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

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