Statistical Analysis Plan	
Study Code	D5180C00019
Edition Number	3
Date	2 September 2020

A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tezepelumab in Japanese Adults and Adolescents with Inadequately Controlled Severe Asthma (NOZOMI)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
CCI	[redacted]
CCI	[redacted]
AE	Adverse Event
AESI	Adverse Events of Special Interest
CCI	[redacted]
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AZ	AstraZeneca
BD	Bronchodilator
BMI	Body Mass Index
BP	Blood Pressure
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTD	Common Technical Document
DAE	Adverse Event Leading to Discontinuation of Investigational Product
DBL	Database Lock
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
ER	Emergency Room
CCI	[redacted]
CCI	[redacted]
GCP	Good Clinical Practice
ICS	Inhaled Corticosteroids
IP	Investigational Product
IPD	Investigational Product Discontinuation
L	Litre
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
CCI	[redacted]

Abbreviation or special term	Explanation
NC	Not Calculable
NQ	Non-quantifiable
OCS	Oral Corticosteroids
PD	Protocol Deviation
CCI [redacted]	
PT	Preferred Term
Q4W	Every 4 Weeks
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TBL	Total Bilirubin
UC	Urgent Care
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
N/A	04Jun2019	Initially Approved SAP	Yes (V2.0)	
Data presentations	28Feb2020	Section 3.1.1: Definition of baseline was made consistent with CSP.	Yes (V2.0)	To be in line with CSP.
Other	28Feb2020	Section 3.1.4: Deleted sentences "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."	N/A	The explanation was deleted for clarity.
Data presentations	28Feb2020	Section 3.1.4: Added the handling of more than one non-missing value within the same visit window for categorical variable case.	N/A	To clarify the handling of data in analysis.
Other	28Feb2020	Section 3.2.2: Reference to "treatment-emergent" was replaced by "occurring during on-treatment period".	N/A	To clarify the handling of AEs with missing or incomplete start date.
Data presentations	28Feb2020	Section 3.2.2: Derivation of exposure adjusted incidence rate for AEs updated.	N/A	In line with AZ guideline on reporting safety data.
Data presentations	28Feb2020	Section 3.2.4: Values below the Lower Limit of Quantification (LLOQ) will be set to LLOQ, instead of LLOQ/2.	N/A	In line with AZ guideline on reporting safety data.
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	28Feb2020	Section 4.2.1: Delete the descriptions related to extension study.	N/A	This study has no extension study. It was mentioned in SAP edition 1 by error.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	28Feb2020	Section 4.2.1: All references to FAS were deleted.	N/A	FAS is not used in this study and was mentioned in error in SAP edition 1.
Data presentations	28Feb2020	Section 4.2.1: Added analysis set to be used for each summary.	N/A	To clarify the analysis set to be used when summarising each variable.
Data presentations	28Feb2020	Section 4.2.1: Clarified that age "at the informed consent" will be summarised.	N/A	To clarify the reference point in which age will be calculated.
Data presentations	28Feb2020	A section for prior and concomitant medication and its associated appendix was added. (Sections 4.2.2 and 8.2)	Yes (V2.0)	To be in line with CSP.
Other	28Feb2020	Sections 4.2.1, 4.2.4.1, and 4.2.4.4: All references to treatment group were deleted.	N/A	This is single arm study and treatment groups were mentioned in error in SAP edition 1.
Data presentations	28Feb2020	Sections 4.2.4.2, 4.2.4.3, 4.2.4.4 and 4.2.6.1: Updated to present visit based summaries over time using the on-study period instead of the on-treatment period	N/A	Required for CSR
Data presentations	28Feb2020	Section 4.2.5.1: Clarified that data during planned treatment period will be summarised.	N/A	To clarify the scope of data to be summarised.
Data presentations	28Feb2020	Sections 4.2.5.2, 4.2.5.3: Clarified that data during on-study period will be summarised.	N/A	To clarify the scope of data to be summarised.
Data presentations	28Feb2020	Section 4.2.6.2: Descriptive statistics were updated to "median, range, 1st and 3rd quartiles".	N/A	To use more appropriate descriptive statistics.
Data presentations	28Feb2020	Section 5: Updated the scope of data to be analysed at the interim analysis.	N/A	To clarify the scope of interim analysis.
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data presentations	02Sep2020	Table 1: Removed time window for Week 2 since there is no Week 2 visit in the study.	N/A	To be in line with CSP visit schedule.
Data presentations	02Sep2020	Section 3.2.2: Added the definition of study adjusted incidence rate for adverse events.	N/A	Required for CSR.
Data presentations	02Sep2020	Section 3.3.1: Time at risk derivation updated to allow the date of last exacerbation status to be considered in derivation.	N/A	To simplify and clarify the text.
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Data presentations	02Sep2020	Section 4.2.4.1: Deleted presentation of SOC for AE summary by causality and maximum intensity.	Yes (V3.0)	To be in line with requirement for CSR.
Data presentations	02Sep2020	Section 4.2.6.1: Clarified data to be included in the summary of serum tezepelumab concentrations.	N/A	To provide clarification for TFLs.
Data presentations	02Sep2020	Section 4.2.6.1: Added the presentation of minimum, median and maximum when there is a value that is NQ.	N/A	To provide clarification for TFLs.
Data presentations	02Sep2020	Section 5: Added time at risk derivation at the time of interim analysis.	N/A	To provide additional clarification on interim analysis-specific derivation of time at risk.
Data presentations	02Sep2020	Added Appendix 8.3 to describe COVID-19 outputs for final analysis.	N/A	Required for CSR to assess the impact of COVID-19 pandemic.

1 STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

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

CCI [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

1.2 Study design

This is an open-label, single arm study designed to evaluate the safety of a 210 mg dose of tezepelumab administered subcutaneously every 4 weeks in Japanese adult and adolescent subjects with inadequately controlled severe asthma. Patients will have a history of at least one exacerbation in the past year and background asthma therapy of medium- or high dose ICS plus at least one additional asthma controller medication (long-acting β2 agonist, [LABA], leukotriene receptor antagonists [LTRA], long-acting muscarinic antagonists [LAMA], cromones, and theophylline) with or without maintenance OCS from screening and throughout the study including the follow-up period.

The study will consist of a screening period of 2 weeks, a treatment period of 52 weeks and a post-treatment follow-up period of 12 weeks.

After the informed consent is obtained, subjects will proceed to a screening period of 2 weeks maximum to allow adequate time for all of the eligibility criteria to be evaluated. Subjects who meet all the eligibility criteria will be registered to a treatment period. Subjects will be

maintained on their currently prescribed ICS and at least one additional asthma controller medication at their dose they entered screening, without change, from screening throughout the treatment period.

1.3 Number of subjects

Approximately 66 Japanese subjects will be registered into the study and receive tezepelumab in order to reach 59 completed. The actual number of Japanese subjects registered into the study will be determined after the confirmation of the number of randomized Japanese subjects in NAVIGATOR study (D5180C00007) to ensure that there are 100 total Japanese subjects who receive tezepelumab for 52 weeks.

2 ANALYSIS SETS

2.1 Definition of analysis sets

All subjects analysis set

This analysis set comprises all enrolled subjects who signed the informed consent form, including screening failures, and will be used for the reporting of disposition.

Registered subjects analysis set

This analysis set comprises all subjects registered to study treatment, irrespective of whether IP was subsequently taken, and will also be used for the reporting of disposition.

2.1.1 Safety analysis set

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

Safety, efficacy and CCI data will be summarised using the safety analysis set.

CCI [redacted]

[redacted]

2.2 Violations and deviations

Only important PDs will be listed and tabulated in the CSR, and only for registered subjects (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 subject's rights, safety or well-being. They may include (but not be limited to):

- Subjects who were registered even though they did not meet key entry criteria

- Subjects who developed withdrawal criteria during the study but were not withdrawn
- Subjects who received an incorrect dose
- Subjects who received an excluded concomitant treatment.

All important PDs will be identified and documented by the study team prior to the database lock.

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

The study non-compliance handling plan (NHP) outlines the management of PDs, and includes the proposed categories of PDs in this trial. Any PDs which are not defined as important will not be reported and discussed in the CSR.

3 PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

3.1.1 Definition of baseline

In general, the last non-missing measurement on or prior to first dose of study treatment will serve as the baseline measurement. 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, they will also be considered in the baseline definitions, provided they remain prior to the date of first dose of study treatment.

3.1.2 Absolute change from baseline

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

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

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

3.1.3 Study periods

The following study periods are defined for analysis purposes:

Screening period

Starting on the date of the first study procedure and ending one day prior to registration (for registered 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 registration (efficacy) / date of first dose of IP (safety) and ending on the date of the Week 52 visit or earlier study withdrawal date (for subjects not followed up until Week 52)

On-treatment period

Starting on the date of registration (efficacy) / date of first dose of IP (safety) and ending on the minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal).

Post-treatment period

Starting one day after the end date of on-treatment period and ending on the study completion or withdrawal date.

On-study period (planned treatment and follow-up)

Starting on the date of registration (efficacy) / date of first dose of IP (safety) and ending on the study completion or withdrawal date.

3.1.4 Visit windows

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

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

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

Data collected at unscheduled or repeat visits will also be included in visit windows, and therefore may be included in summaries or analyses by visit.

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. For categorical variables in this situation, the worst case will be used.
- If there are multiple ADA samples in the same visit window with both positive and negative results, the sample with a positive result and the highest titer value should be selected.

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

The same visit window definitions below will be used regardless of whether the planned treatment period or the on-treatment period is used for analysis (see Section 3.1.3). 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 analysis, any off-treatment assessments measured at a follow-up visit (scheduled 16 weeks after last IP administration) which occurred earlier than scheduled follow-up visits Week 58 or Week 64 will be considered in earlier planned treatment period visit windows, where applicable.

Table 1 summarises the visit windows to be used for all variables unless specified otherwise. It corresponds to the full (mostly 4-weekly) protocol scheduling for clinic visits, and will be used for all variables by default, including those variables which are not captured at every clinic visit.

Table 1 Visit windows – all variables where not specified otherwise

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

3.1.5 Prior and concomitant medication

Medications taken by any subject at any time during the study will be coded using the ATC classification system within the WHO Drug Dictionary.

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

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

– start date > date of last dose of IP + 33 days.

Essentially the above says that:

- Prior and concomitant medications are mutually exclusive.
- Concomitant medications on-treatment and post-treatment are also mutually exclusive (here, the word "concomitant" means concomitant with study procedures, irrespective of whether IP was still being taken). Specifically, a concomitant medication which started on-treatment and ended post-treatment will only be considered on-treatment.

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

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

3.2 Derivation of safety variables

3.2.1 Exposure to IP and treatment compliance

Extent of exposure to IP will be calculated as follows:

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 will be derived as the sum of the individual subject extents of exposure (days) 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.

3.2.2 Adverse events - general

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

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

- AEs occurring during screening 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.

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

Exposure adjusted incidence rates will be defined as the number of subjects reporting adverse events divided by extent of exposure for each subject, where exposure will be defined (irrespective of whether they have had the AE) as in 3.2.1 for extent of exposure for the on-treatment summaries.

Study adjusted incidence rates will be defined as the number of subjects reporting adverse events divided by duration of the on-study period for each subject as defined in Section 3.1.3.

The total time at risk (years) will be derived as the sum of the individual subject times at risk (days) divided by 365.25.

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

3.2.3 Adverse events of special interest

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

3.2.4 Laboratory variables

Clinical chemistry, haematology and urinalysis will be performed by local laboratories according to the schedule and the variable specifications described in the CSP.

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

In all 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 included in the analysis.

Absolute values will be compared to the relevant normal reference range, as provided by the central laboratory, and classified as low (below range), normal (within range or on the limits) or high (above range). All values falling outside the normal reference ranges will be flagged. These classifications will also be used for shift tables.

For the purposes of shift tables, baseline will be defined as specified in Section 3.1.1. Minimum, maximum and last values calculated across all visits in the relevant study period will use all available values including those from unscheduled and repeat visits, and irrespective of whether the values have been selected for use in summaries using visit windows (see Section 3.1.4).

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

- AST $\geq$ 3 x ULN
- ALT $\geq$ 3 x ULN
- TBL $\geq$ 2 x ULN

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

3.2.5 Vital signs

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

BMI is calculated as:

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

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

Table 2 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit	Change from Baseline Criteria
Diastolic BP (sitting)	mmHg	60	100	±15
Systolic BP (sitting)	mmHg	90	160	±30
Pulse rate (sitting)	beats/min	50	100	±20
Respiratory rate	breaths/min	8	20	
Body temperature	Celsius	36.0	37.5	
Weight	kg	40	150	

3.2.6 12-lead ECG

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

Changes from baseline in continuous 12-lead ECG variables (data provided external to the eCRF) will be calculated at relevant visits as specified in Section 3.1.1 and Section 3.1.2.

3.2.7 Physical examination

No physical examination results are captured in this trial, unless judged a new clinically significant finding or a clinically significant aggravation of an existing finding by the investigator, and consequently reported as an AE.

3.2.8 Medical history

If a partial diagnosis date is available only, the following rules will be used to impute a complete date (e.g. for derivation of time since diagnosis):

If both the month and the year are available, the first of the recorded month will be imputed, unless the date of birth is within the same month and year (where date of birth is available, which will not be the case in all countries). In this case, the date of birth will be imputed instead.

If only the year is available, 1st January will be imputed, unless the date of birth is within that same year (where date of birth is available). In this case, the date of birth will be imputed instead.

3.3 Derivation of efficacy variables

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4 ANALYSIS METHODS

4.1 General principles

All data will be summarised using appropriate descriptive statistics. No statistical hypothesis tests will be made.

4.2 Analysis methods

4.2.1 Subject disposition, demography and baseline characteristics

Subject disposition will be summarised using the all subjects analysis set. The number of enrolled subjects will be summarised. The number and percentage of subjects will be presented by the following categories; registered, not registered (and reason), received IP, did not receive IP (and reason), completed treatment, discontinued treatment (and reason), completed study (subjects who completed IP and study, and subjects who discontinued IP but completed study assessments), and discontinued study (including reason). Subject recruitment by centre will be summarised using registered subjects analysis set.

The number and percentage of subjects, who discontinued IP, but remained in the study will be presented and option of follow up using safety analysis set.

Demographic data such as age at informed consent, gender, and race will be summarised using safety analysis set.

Various baseline characteristics will also be summarised using safety analysis set. These include medical, surgical and respiratory disease histories, weight, height and BMI, smoking status, history of allergy, pre-BD FEV_1, asthma duration, age at onset of asthma, asthma medications, the number of asthma exacerbations in the previous 12 months, number of asthma exacerbations requiring hospitalisations in the previous 12 months, and ACQ 6.

Medical and surgical histories will be summarised using safety analysis set by MedDRA Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA.

Important PDs will be summarised using safety analysis set.

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

4.2.2 Prior and concomitant medication

The number and percentage of subjects receiving each medication (by ATC classification system codes and generic name) will be presented by treatment for the safety analysis set. Separate tables will be presented for all medications received during each of the following

periods as defined in Section 3.1.5: 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 ICS medications. The number of subjects using other maintenance asthma medications at baseline will also be summarised. In addition, the total number of days of systemic corticosteroid treatment associated with asthma exacerbations per patient from the first day of IP up to Week 52 will also be summarised.

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

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

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

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

Percentages will be calculated relative to the number of subjects in the safety analysis set.

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

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

4.2.3 Exposure and compliance

Exposure and treatment compliance derivation details are defined in Section 3.2.1.

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

The date and time of IP administrations, and all missed doses will be listed using the safety analysis set.

4.2.4 Safety analysis

All safety variables will be summarised using the safety analysis set (see Section 2.1.1 for details).

4.2.4.1 Adverse events

AEs will be summarised separately for the on-treatment and on-study periods as defined in Section 3.1.3 unless stated otherwise. AEs occurring during the screening period, or occurring post-treatment will be listed, but not summarised separately.

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

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

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

- SAEs
- Fatal AEs
- DAEs
- DAEs causally related to IP
- Each AESI category separately
- The most common AEs (defined as those occurring in >3% of subjects) – by PT only

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

In addition, each AESI category will be summarised by causality.

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

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

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

- All AEs
- Each AESI separately

In these summaries, the exposure-adjusted rate will be defined as the number of subjects reporting the AE divided by the total time at risk for all subjects, the latter as defined in Section 3.2.2. Rates will be reported as events per 100 subject-years.

4.2.4.2 Laboratory data

All continuous laboratory variables will be summarised by absolute value at each visit, together with the corresponding changes from baseline. These summaries will be produced for the on-study period, as defined in Section 3.1.3. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted.

Local 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, high and missing values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

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

Both shift tables and shift plots will be produced using all data for the on-study period, as defined in Section 3.1.3.

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

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

For all subjects who meet the biochemical criteria for Hy's Law (potential Hy's Law cases), the relevant laboratory variables will be tabulated showing all visits for these subjects. Subjects with elevated ALT or AST in addition to elevated TBL at any time may be explored further graphically using individual subject profile plots.

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

4.2.4.3 Vital signs

All vital signs variables will be summarised by absolute value at each visit, together with the corresponding changes from baseline. This will also include weight and BMI. These summaries will be produced for the on-study period, as defined in Section 3.1.3. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

AZ-defined reference ranges (see Section 3.2.5) will be used for the identification of individual abnormalities. A shift table will be produced for each vital signs variable to display low, normal, high and missing values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

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

Both shift tables and shift plots will be produced using all data for the on-study period, as defined in Section 3.1.3.

Subjects who have changes from baseline outside the pre-defined AZ clinically important change criteria in Section 3.2.5 will be summarised. All data for the on-study period will be used.

4.2.4.4 12-lead ECG

Continuous 12-lead ECG variables will be summarised by absolute value at each visit, together with the corresponding changes from baseline. These summaries will be produced for the on-study period, as defined in Section 3.1.3. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD.

A shift table will be produced to display the investigator assessment of normal, abnormal – not clinically significant, abnormal – clinically significant and not done between baseline and end of study. For this purpose, borderline (also recorded on the eCRF) will be grouped with normal.

A frequency table showing subjects with corrected QT (QTc) values and increases from baseline at any time during the on-study period using standard pre-specified thresholds will be produced.

4.2.4.5 Physical examination

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

4.2.5 Efficacy analysis

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

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4.2.6 Pharmacokinetics and immunogenicity

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- CCI [redacted]

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5 INTERIM ANALYSES

An interim analysis to summarise 6 months safety data will be performed when all subjects complete Visit 8 (24-week of treatment period) for submission.

In principle, all data up to and including 182 days after the first dose of IP will be summarised according to methods described in this document. When calculating exposure and on-treatment period, the following end date will be used: minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal, date of first dose of IP +182 days). When calculating other study periods, date of first dose of IP + 182 will be used instead of completion date. When calculating the time at risk for asthma exacerbation (Section 3.3.1), "registration date + 182 days" will be used instead of "date of Visit 15" and "registration date + 364 days + 5 days".

6 CHANGES OF ANALYSIS FROM PROTOCOL

None.

7 REFERENCES

CCI [redacted]

CCI [redacted]

Sampson et al., 2006
Sampson H.A, A. Munoz-Furlong, R.L. Campbell, N.F. Adkinson Jr., S.A. Bock, A. Branum et al. Second symposium on the definition and management of anaphylaxis: summary report: Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 117 (2006), pp. 391–397.

Takase et al., 2008
Takase M, Sakata H, Shikada M, Tatara K, Fukushima T, Miyagawa T. Nihonjinshōni niokeru supairoguramu-kijyunchi no sakusei (saishūhōkoku) [Creation of reference value for spirogram in Japanese paediatrics (final report)]. Japanese Journal of Pediatric Pulmonology. 2008, 19 (2), pp.164-176 (in Japanese).

8 APPENDIX

8.1 Adverse events of special interest

8.1.1 Anaphylactic reactions

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

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

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

8.1.2 Immune complex disease (Type III hypersensitivity reactions)

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

8.1.3 Malignancy

Malignancy will be defined on the basis of an SMQ.

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

8.1.4 Helminth infections

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

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

8.1.5 Severe infections (as defined in the protocol)

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

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

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

8.1.6 Injection site reactions

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

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

8.1.7 Opportunistic infections

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

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

8.1.8 Guillain-Barre syndrome

Guillain-Barre syndrome will be defined using an SMQ.

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

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

8.2 OCS conversion factors for prednisone equivalents

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

Table 3 Estimated OCS dose therapy equivalence

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

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

8.3 Additional reporting to assess the impact of the COVID-19 pandemic

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

Section 2.2 Violations and Deviations

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

An additional summary will be provided of IPDs related to COVID-19, and IPDs excluding COVID-19 related IPDs for the safety analysis set.

Section 4.2.1 Subject disposition, demography and baseline characteristics

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

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

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

Section 4.2.3 Exposure and Compliance

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

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Section 4.2.4.1 Adverse Events

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

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

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

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