STATISTICAL ANALYSIS PLAN

Study Code	D7930C00002
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A Phase 2a, Randomised, Single-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics and Explore the Pharmacodynamic Effects of AZD2389 in Participants with Liver Fibrosis and Compensated Cirrhosis (BORANA)

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units. Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/transaminase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase/transaminase
ATC	Anatomical Therapeutic Chemical
BP	Blood pressure
CCI	
CI	Confidence interval
CK	Cytokeratin
CLD	Chronic liver disease
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CCI	
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
CCI	
FAP	Fibroblast Activation Protein
FAS	Full analysis set
CCI	
gCV	Geometric coefficient of variation
GGT	Gamma-glutamyl transferase
Gmean	Geometric mean
HA	Hyaluronic acid
HbA1c	Haemoglobin A1C
CCI	
hsCRP	High sensitivity C reactive protein
CCI	
ICH	Internation council for harmonisation

Abbreviation or Specialized Term	Definition
IP	Investigational Product
IPD	Important Protocol Deviation
CCI	
LLOQ	Lower limit of quantification
CCI	
MASH	Metabolic dysfunction-associated steatohepatitis
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Models for Repeated Measures
NASH	Nonalcoholic steatohepatitis
NTproBNP	N-terminal Prohormone of Brain Natriuretic Peptide
CCI	
PEth	Phosphatidylethanol
PK	Pharmacokinetics
PIIINP	Procollagen 3 n-terminal propeptide
CCI	
PT	Preferred term
QTCF	QT interval corrected for heart rate using Fridericia's formula (QTcF)
RR	Respiratory rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation
SoA	Schedule of activities
SOC	System organ class
SpO2	Oxygen saturation
CCI	
T4	Free Thyroxine
TBL	Total bilirubin
CCI	
TIMP1	Tissue inhibitor of metalloproteinase 1
TSH	Thyroid-stimulating Hormone
ULN	Upper limit of normal

Abbreviation or Specialized Term	Definition
ULOQ	Upper limit of quantification
CCI	
WHO DD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	3/7/2025	Initial approved SAP	N/A	N/A
Other endpoints.	8/11/2025	Inclusion of u-creatinine in Section 4.2.1.4 as per latest version of protocol.	Yes	Protocol was amended to include u-creatinine. This is now included in the analysis.
Other endpoints.	8/11/2025	Abbreviation added for Rac Cmax in Section 4.2.2.2	Yes	Rac Cmax is part of objective 2 and needed to be included in the abbreviations.
Other endpoints.	8/11/2025	Parameter derivations included in Section 4.2.1.2, 4.2.3.4.5 and 4.2.3.4.6, with references added to Section 6.	Yes	Updated to include derivations for CCI [redacted]
Other endpoints.	8/11/2025	Updated to include CCI [redacted] in Section 4.2.3.4.5. Updated to include respiratory rate normal range.	Yes	Following dry run, CCI [redacted] were requested for summary statistics. Normal range was also given for respiratory rate.
Other endpoints.	8/19/2025	FAP activity derivation added to Section 4.2.2.4.2. CCI [redacted] added to Section 4.2.3.4.4.	Yes	Concentrations/peptides received from vendor and required derivations to produce FAP activity/ CCI [redacted]
Disposition	8/28/2025	Removed ongoing status derivation from Section 4.1.1.1	Yes	Updated following request from dry run.

Other endpoints.	9/5/2025	CCI [redacted] adjusted to CCI [redacted] due to being collected as a concentration. See Sections 2 and 4.2.3.4.3.	Yes	CCI [redacted] adjusted to CCI [redacted] for consistency with data collected.
Other endpoints.	9/9/2025	CCI [redacted] analysis updated to ANCOVA instead of MMRM in Section 4.2.1.4.	Yes	Analysis updated due to issues with samples at visits 4, 5 and 8.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D7930C00002 supporting the clinical study report (CSR).

This statistical analysis plan (SAP) is based on version 4.0 of the clinical study protocol (CSP) that was finalised on 17th April 2025.

This is a Phase 2a, randomised, single-blind, placebo-controlled study to evaluate the safety, tolerability, and pharmacokinetics and explore the pharmacodynamic effects of AZD2389 in participants with liver fibrosis and compensated cirrhosis. AZD2389 will be evaluated in two cohorts, each with a parallel-group design and two arms, with participants blinded to treatment allocation. Cohort A will consist of participants with presumed metabolic dysfunction-associated steatohepatitis (MASH)/ nonalcoholic steatohepatitis (NASH) with fibrosis. CCI Cohort B will include participants with underlying steatotic liver diseases of varying aetiologies (eg, Metabolic and alcohol-related liver disease, Alcohol-related liver disease, and treated hepatitis C virus) and have advanced fibrosis including compensated cirrhosis (F3-cF4).

The total duration of study participation for each participant in Cohorts A and B will be approximately 63 days (9 weeks) and will include an up to 28-day screening period, a 28-day treatment period, and a follow-up visit seven days following completion of treatment. Assessments will be conducted as described in the protocol schedule of activities (SoA).

The dose of AZD2389 used in this study was concluded to be CCI , at a dose range that covers the planned dose in the current study. The definition of CCI CCI is that none of the CCI .

Note: throughout the CSP the term ‘participants’ is used, however all AstraZeneca output standards use ‘subjects’, therefore the description of the outputs is provided for ‘subjects’ in this SAP.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Exploratory endpoint evaluating the effects of AZD2389 on CCI CCI in protocol mentions CCI . This is replaced by CCI for statistical analysis due to being collected as a concentration.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Final analysis is performed after the clinical database lock. Final analysis results are used to write the CSR.

3.2 Analysis Populations

The following populations are defined:

Table 1 – Populations for Analysis

Population/Analysis set	Description
Enrolled	All subjects who have a validly signed informed consent form.
Full Analysis Set (FAS)	The FAS consists of all subjects who are randomised and receive at least one dose of study intervention. Subjects are evaluated according to the treatment assigned at randomisation. The FAS is used for all analyses of demographic and baseline characteristics, and efficacy data.
Safety Analysis Set (SAF)	The SAF consists of all subjects who are randomised and receive at least one dose of study intervention. Erroneously treated subjects are accounted for in the study intervention cohort of the study intervention they actually receive. The SAF is used as the primary population for reporting safety data.
Pharmacokinetic (PK) Analysis Set	The PK analysis set includes all subjects who receive AZD2389 and have at least one evaluable (including concentrations reported as < lower limit of quantification [LLOQ] after first dose) PK concentration. The exclusion of any subjects or timepoints from the calculation of the PK parameters is documented by the Clinical PK Scientist including the reason(s) for exclusion.

3.3 General Considerations

- Outputs are summarised by cohort, treatment group and overall where appropriate, including summary of placebo and AZD2389 separately pooled across cohorts.

- All variables are summarised using descriptive statistics as appropriate. Continuous variables are summarised by the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.

- For log-normal continuous variables, descriptive statistics includes n, mean, SD, median, minimum, maximum and geometric mean (gmean) and geometric coefficient of variation (gCV).

- Categorical variables are summarised by number of observations and percentages for each category. Changes from baseline in categorical data are summarised using shift tables where appropriate.

- Summary statistics are not calculated if there are 3 or less observations for a continuous variable, with the exception of number of observations, minimum, and maximum.

- Unless otherwise stated, percentages are calculated based on the population total and for the corresponding treatment group in cohort in the analysis set being presented.

- For continuous data, the mean, median and SD are rounded to 1 additional decimal place compared to the original data. Minimum and maximum are displayed with the same accuracy as the original data.

- For categorical data, percentages are rounded to 1 decimal place. Percentages are not presented for zero counts.

- P-values greater than or equal to 0.001, in general, are presented to three decimal places. P-values lower than 0.001 are presented as "<0.001".

- Confidence intervals (CIs) are presented to one more decimal place than the raw data.

- SAS® version 9.4 or above is used for all analyses.

3.3.1 General Study Level Definitions

Study Day

All assessment days are related to the day of first dose of study intervention.

Day 1 is defined as the day of the first dose of study intervention. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

Baseline

Baseline for statistical analyses is defined as the last assessment of the variable under consideration prior to the administration of the first dose of study intervention. Assessments carried out on day of the first dose are considered to have taken place before the first dose of study intervention, if the corresponding times have not been recorded.

Post-baseline

Post-baseline for statistical analyses is defined as any assessment taken post first dose of study intervention.

Change and Percent Change from Baseline

In all summaries change from baseline is calculated as:

Change from baseline = post-baseline value – baseline value.

Percentage change from baseline is calculated as:

Percent change from baseline = [(post-baseline value – baseline value) / baseline value] × 100.

If either a post-baseline visit value or baseline value is missing, the absolute change from baseline and the percent change from baseline are set to missing.

On-treatment Assessment

On-treatment assessments include:

- On the date of first dose of study intervention if assessment time is recorded, and it is after the first dosing time.
- After the date of first dose of study intervention up to and including 7 days after the last dose of study intervention, scheduled on Visit 8 (Follow-up)

End of Study

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the protocol SoA.

3.3.2 Imputation of Missing Dates

No imputations are done for missing or partial missing dates, except for the start and end dates for AEs, and prior and concomitant medication, which are imputed as indicated below.

Partial/Missing Start Date

Missing day – Impute the 1st of the month unless month is same as month of first dose of study intervention, then impute first dose date.

Missing day and month – Impute 1st January unless year is the same as first dose date, then impute first dose date.

Completely missing – Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date ensure that the new imputed date is sensible, i.e., prior to the end date of the AE or medication.

Partial/Missing End Date

Missing day – Impute the last day of the month unless month is same as month of last dose of study intervention then impute last dose date

Missing day and month – Impute 31st December unless year is the same as last dose date then impute last dose date

Completely Missing – If the ongoing flag is missing then assume that AE is still present / medication is still being taken, i.e., do not impute a date. If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute as date of last visit.

When imputing an end date ensure that the new imputed date is sensible, i.e., on or after the start date of the AE or medication.

3.3.3 Visit Window

All data is analysed using nominal study visit as defined in the protocol SoA and electronic Case Report Form (eCRF).

3.3.4 Handling of Unscheduled Visits

Unscheduled visit data is included in the listings and presented in the summary tables when appropriate.

3.3.5 Multiplicity/Multiple Comparisons

No multiplicity adjustments are applicable as statistical comparisons are for exploratory purposes only.

3.3.6 Handling of Protocol Deviations in Study Analysis

Protocol deviations being classified as Important Protocol Deviations (IPD) include deviations related to:

- Inclusion criteria
- Exclusion criteria
- Discontinuation criteria for study product met but subject not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study
- Excluded medication taken
- Investigational product deviation
- Deviations related to study procedure
- Other important protocol deviations

Details regarding protocol deviations, including a finer sub-categorization, as well as methods of detection, are found in the protocol deviation plan and the protocol deviation list. Since main analyses are performed according to the safety analysis set, occurrence of an IPD does not imply exclusion of data from these analyses.

3.3.7 LLOQ and Upper Limit of Quantification (ULOQ)

Laboratory tests below the LLOQ for which the exact value cannot be determined, are replaced with the LLOQ/sqrt(2) value. Similarly, laboratory test results above the upper limit of quantification (ULOQ) for which the exact value cannot be determined, are replaced with the ULOQ value. After the LLOQ/ULOQ replacement, change from baseline to each post-baseline visit is defined as the post-baseline visit value minus the baseline value. After the LLOQ/ULOQ replacement are also classified as normal (if value is within normal reference range), low (if value is below the normal reference range), high (if value is above the normal reference range) based on the reference range indicator. Tables utilise

the LLOQ/ULOQ replacement. However, listings display the original LLOQ/ULOQ inequality (e.g., "<x" and ">x").

4 STATISTICAL ANALYSIS

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

4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication and study intervention compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

A subject is considered as screened/enrolled if the main informed consent date is collected in the eCRF.

A subject is considered as started treatment if at least one dose of study intervention was taken. A subject is considered as completed treatment if subject's status is recorded as 'Completed' in the eCRF. A subject with any other non-missing status is considered as discontinued from the treatment.

A subject is considered as completed study if subject's status is recorded as 'Completed' in the eCRF. A subject with any other non-missing status is considered as discontinued from the study.

4.1.1.2 Presentation

Subject disposition is reported as follows:

- Number of subjects screened
- Number of subjects randomised
- Number and percentage of subjects in the following categories:
  - Subjects started treatment
  - Subjects completed treatment
  - Subjects discontinued treatment, including reasons for treatment discontinuation
  - Subjects completed study
  - Subjects withdrawn from study, including reasons for study discontinuation.

Disposition is listed for the Enrolled Set.

Recruitment by country and site is also presented.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The definitions of all analysis sets used in the study are provided in the Section 3.2.

4.1.2.2 Presentation

Analysis sets are summarised as follows:

- Number of subjects included in each analysis set
- Number of subjects excluded from the analysis set together with the reasons for exclusion

A listing of non-screen failure subjects excluded from at least one analysis set is presented.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

In accordance with International Council for Harmonisation (ICH) E3 a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

4.1.3.2 Presentation

Important protocol deviations are reported for the FAS as follows:

- The number and percentage of subjects:
  - With at least one important protocol deviation
  - In each IPD category:
    - Inclusion/Exclusion criteria
    - Discontinuation criteria for study product met but subject not withdrawn from study treatment
    - Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study
    - Investigational product deviation
    - Excluded medication taken
    - Deviations related to study procedure
    - Other important protocol deviations

Subjects deviating from a criterion more than once are counted once for that criterion. Any subjects who have more than one IPD are counted once in the overall summary.

Important protocol deviations are listed for the FAS.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The following demographic data is collected:

- Age (years),
- Sex (Male/ Female),
- Ethnicity (Hispanic/ Latino/ Not Hispanic/Latino),
- Race (Black or African American/ Native Hawaiian or other Pacific Islander/ American Indian or Alaska Native/ Asian/ White/ Other/ Not reported).

The age (in years) is categorised into the following groups:

- 18 to < 65,
- ≥ 65.

4.1.4.2 Presentation

Demographic data is reported for the FAS, and analysed as described in Section 3.3:

- Standard descriptive statistics are presented for the continuous variables.
- Number and percentage of subjects are presented for categorical variables.

All missing data is presented as part of a missing category, if appropriate.

Demographic characteristics are listed for the FAS.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Weight (kg), height (cm) and body mass index (BMI) (kg/m2) baseline to be derived based on baseline definition in Section 3.3.1.

4.1.5.2 Presentation

Baseline characteristics are reported for the FAS, and analysed as described in Section 3.3 using standard descriptive statistics for the continuous variables.

Baseline characteristics are listed together with demographic data for the FAS.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Not applicable.

4.1.6.2 Presentation

Not applicable.

4.1.7 Medical/Surgical History

4.1.7.1 Definitions and Derivations

Medical history includes medical history term, start date and stop date (or ongoing if applicable), and any current medication (yes/no).

Surgical history data includes surgical procedure term, start date and current medication (yes/no).

4.1.7.2 Presentation

Medical/surgical history are coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

Medical/surgical history is reported for the FAS.

The number and percentage of subjects with any relevant medical/surgical history is presented by system organ class (SOC) and preferred term (PT) by treatment group within cohort. Subjects with multiple medical or surgical history occurrences within the same SOC/PT are counted once per SOC and PT regardless of the number of occurrences. The summary is sorted by descending order of overall numerical counts for SOC and PT. Where there are ties, they are sorted alphabetically.

Medical/surgical history data is listed by cohort, subject, start date and term for the FAS.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior and concomitant medications are defined as follows:

- Prior medications are those taken prior to enrolment with a stop date prior to the first dose of study intervention.
- Concomitant medications are those with a start date on or after the first dose of study intervention, or those with a start date before the first dose of study intervention and either a stop date on or after the first dose of study intervention, or are ongoing at the end of the study.

See Section 3.3.2 for partial/missing date imputations for derivation of prior/concomitant medication category.

See CSP appendix F for list of disallowed medications.

4.1.8.2 Presentation

All medications are coded using the latest version of World Health Organization Drug Dictionary (WHO DD), Format B3, Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior/concomitant medications/concomitant disallowed medications are reported for the FAS as follows:

- The number and percentage of subjects with at least one prior / concomitant / concomitant disallowed medications
- The number and percentage of subjects with at least one prior / concomitant / concomitant disallowed medications within each ATC classification and generic drug term.

Subjects are counted once per ATC classification and generic drug name regardless of the frequency of medication usage.

The summary is sorted in descending order of overall numerical counts for ATC classification and generic drug term, or by descending order of numerical counts for SOC and PT, as appropriate. Where there are ties they are sorted alphabetically.

Prior and concomitant medications are listed for the FAS.

4.1.9 Study Intervention Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance is a measure of how much study intervention is taken relative to how much study intervention should have been taken given the subjects time on study.

Treatment compliance (%) is calculated as: $\frac{\text{CCI [redacted]}}{\textit{Number of days on treatment}\text{ CCI [redacted]}} \times 100$

Where,

- CCI [redacted], as each subject is required to take CCI mg and CCI mg CCI [redacted].

The calculated compliance (%) is categorised as:

- <80
- 80 to <= 120
- > 120

4.1.9.2 Presentation

Treatment compliance is reported for the FAS as follows:

- Standard descriptive statistics are presented for the continuous variable
- Number and percentage of subjects in each compliance category.

The study intervention administration is listed for the safety analysis set.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Table 2 - Endpoints

Statistical category	Endpoint	Population	Details in section
Objective 1: To assess the safety and tolerability of AZD2389 following oral administration in participants with chronic liver disease (CLD) and hepatic fibrosis			
Primary	AEs	SAF	4.2.1
	Vital signs (Blood pressure, pulse rate, oxygen saturation [SpO2], body temperature, and respiratory rate)		
	12-lead safety electrocardiogram (ECG)		
	Physical examination		
	Laboratory assessments (haematology, coagulation, clinical chemistry, CCI , and urinalysis)		
Objective 2: To characterise the PK of AZD2389 in participants with CLD and hepatic fibrosis			
Secondary	Plasma and urine PK parameters of AZD2389	PK Analysis Set	4.2.2
	Cmax, Tmax, Tlast, AUClast, AUCinf, AUCtau, t1/2λz, Vz/F, CL/F, TCP, Rac Cmax, Rac AUC, CLR, Ae, and Fe.		
Objective 3: To evaluate the effect of AZD2389 on plasma FAP activity following oral administration of AZD2389 in participants with CLD and hepatic fibrosis			
Secondary	Inhibition of fibroblast activation protein (FAP) activity at Days 1, 7, 14, 28, and follow-up (calculated as change and percentage change in FAP activity against baseline) compared to placebo	FAS	4.2.2
Objective 4: To evaluate effects of AZD2389 on CCI			

Table 2 - Endpoints

Statistical category	Endpoint	Population	Details in section
CCI following oral administration of AZD2389 in participants with chronic advanced liver disease			
Exploratory	Change and percentage change from CCI in CCI and CCI CCI compared to placebo as assessed by CCI	FAS	4.2.3
Objective 5: Optional as per site capability: To evaluate effects of AZD2389 on CCI CCI following oral administration of AZD2389 in participants with compensated advanced liver disease			
Exploratory	Change and percentage change from CCI in CCI compared to placebo as assessed by CCI	FAS	4.2.3
Objective 6: To evaluate effects of AZD2389 on CCI			
Exploratory	Change and percentage change from CCI compared to placebo in: CCI	FAS	4.2.3
Objective 7: To evaluate the effects of AZD2389 on CCI			
Exploratory	Change and percentage change from CCI compared to placebo in: CCI	FAS	4.2.3
Objective 8: To evaluate effects of AZD2389 on CCI			
Exploratory	Change and percentage change from CCI CCI compared to placebo in: CCI Not included in CSR • CCI	FAS	4.2.3

Table 2 - Endpoints

Statistical category	Endpoint	Population	Details in section
	• CCI		
Objective 9: To evaluate effects of AZD2389 on CCI			
Exploratory	Change and percentage change from CCI compared to placebo in: CCI	FAS	4.2.3
Objective 10: To evaluate effect of AZD2389 on CCI			
Exploratory	Change and percentage change from CCI compared to placebo in: CCI	FAS	4.2.3
Objective 11: Optional: To collect and store plasma and serum samples for future research. **Note: This optional sample is taken from consented participants.**			
Exploratory	Results are not reported in the CSR.		Not covered in SAP
Objective 12: Optional: To explore how multi-omics variations, including genetics, may affect CCI . **Note: The samples are taken from consented participants for deoxyribonucleic acid (DNA) and blood derivatives** **isolation and storage.**			
Exploratory	Exploratory endpoints are related to the data generated from multi-omics analysis, including genetics CCI . (Results are not reported in the CSR.)		Not covered in SAP

4.2.1 Primary Endpoint

4.2.1.1 Definition

Primary endpoints are listed in the Table 2 in Section 4.2.

4.2.1.2 Derivations

On-treatment assessment definition is provided in Section 3.3.1.

Albumin-corrected calcium[7] is derived as follows,

$$\text{Alumin} - \text{corrected calcium (mg/dL)} = 0.8 * (40 - \text{Albumin [g/L]}) + \text{Calcium (mg/dL)}$$

$$\text{Alumin} - \text{corrected calcium (mmol/L)} = 0.02 * (40 - \text{Albumin [g/L]}) + \text{Calcium (mmol/L)}$$

4.2.1.3 Handling of Dropouts and Missing Data

In general, missing data of AEs, clinical laboratory, vital signs, and ECG are not imputed.

AEs with missing relationship to treatment are considered related to treatment.

4.2.1.4 Primary Analysis of Primary Endpoint

Primary endpoints are reported for the SAF.

Adverse Events

Adverse events are coded using the latest version of MedDRA.

Unless otherwise specified, only AEs with an onset date on or after first dose of investigational product (IP) up to and including 7 days following the date of last IP are presented in summary tables. Pre-treatment AEs are considered as AEs with an onset date before first dose of IP.

Overall summary of adverse events is reported as follows:

- Number and percentage of subjects experiencing:
  - Any AE
  - Any SAE
  - Any SAE with outcome death
  - Any AE leading to discontinuation of IP
  - Any possibly related SAEs

- Count of events in the following categories:
  - All AEs
  - All SAEs
  - All SAEs with outcome death
  - All AEs leading to discontinuation of IP
  - Any possibly related SAEs

Separate tables by SOC and PT covering number and percentage of subjects reporting at least one event are presented for the following types of AEs:

- AEs
- AEs by maximum intensity
- Possibly related SAEs
- SAEs
- SAEs with outcome of death
- Pre-treatment SAEs
- AEs leading to discontinuation of IP

In the summaries, subjects with more than one event within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT, respectively.

For summaries by maximum intensity, subjects with multiple events within a particular SOC or PT are counted under the category of their most severe AE within that SOC or PT. AEs with missing intensity are included in the counts of the 'Number of subjects with at least one event', 'System Organ Class' and 'Preferred Term' rows of the summary but they are not included in the counts by intensity.

Summaries by SOCs and PTs are sorted by descending order of overall numerical counts. Where there are ties, they are sorted alphabetically.

Key information is presented for subjects with SAEs with outcome of death, SAEs, and AEs leading to discontinuation of IP.

An AE listing for the SAF covers details for each individual AE.

Laboratory

The following laboratory parameters are collected:

Table 3 - Clinical Laboratory Evaluation

Standard Clinical Laboratory Evaluation: Haematology	
B-haemoglobin	B-mean corpuscular haemoglobin concentration
B-haematocrit	B-neutrophils
B-leucocyte count	B-lymphocytes
B-platelet count	B-monocytes
B-erythrocytes	B-eosinophils
B-mean corpuscular volume	B-basophils
B-mean corpuscular haemoglobin	
Standard Clinical Laboratory Evaluation: Serum Clinical Chemistry	
Creatinine (Cr)	Alkaline phosphatase

Estimated glomerular filtration rate (calculated based on Cr)	Gamma-glutamyl transferase
Blood urea nitrogen	Albumin
Potassium	Calcium, total
Sodium	Albumin-corrected calcium[7]
Alanine aminotransferase	Phosphate
Aspartate aminotransferase	Creatine Kinase
Total Bilirubin	
Standard Clinical Laboratory Evaluation: Urinalysis	
U-haemoglobin/erythrocytes/blood	U-nitrites
U-leukocytes	U-colour
U-protein/albumin	U-clarity
U-glucose	U-pH
U-bilirubin	U-specific gravity
U-ketones	U-creatinine
Standard Clinical Laboratory Evaluation: Coagulation	
Activated partial thromboplastin time	Prothrombin time
International normalised ratio	
Clinical Laboratory Evaluation: Additional Clinical Chemistry	
Thyroid-stimulating Hormone (TSH)	N-terminal Prohormone of Brain Natriuretic Peptide (NTproBNP)
Free Thyroxine (T4)	Lipase
Clinical Laboratory Evaluation: Whole blood	
Haemoglobin A1C (HbA1c)	Phosphatidylethanol (PEth)

CCI

On-treatment clinical laboratory results received from central laboratory are summarised by treatment group within cohort and for the combined cohorts as described in Section 3.3.

All haematology and clinical chemistry (Including NTproBNP and PEth) parameters are reported for each scheduled post-baseline visit (Including follow-up) as follows:

- The descriptive statistics are presented for observed values and change from baseline.
- The frequency tables present number of subjects with their laboratory status (e.g., low, normal, high)

Shift tables present laboratory status (low, normal, high) from baseline to maximum and minimum post-baseline value.

Key information is also presented for subjects with haematology and chemistry (Including NTproBNP and PEth) abnormalities.

For categorical urinalysis results, treatment emergent increase in urinalysis defined as change from negative/trace at baseline to ++, +++, or ++++ at any visit after baseline or an increase of at least ++. For continuous results, treatment emergent is defined as a value that was normal at baseline but low or high while on-treatment.

Urinalysis parameters are reported as follows:

- Shift tables are presented from baseline to maximum post-baseline while on-treatment value (Normal, trace, +, ++, +++, ++++).

A tabulation of treatment emergent abnormalities are also presented for chemistry (Including NTproBNP and PEth), haematology, and urinalysis parameters.

Elevation in liver parameters for assessment of Hy's Law are reported as follows:

- Alanine aminotransferase (ALT)
  - ≥ 3x – ≤ 5x upper limit of normal (ULN)
  - > 5x – ≤8x ULN
  - > 8x – ≤ 10x ULN
  - > 10x – ≤ 20x ULN
  - > 20x ULN

- Aspartate aminotransferase (AST)
  - ≥ 3x – ≤ 5x ULN
  - > 5x – ≤ 8x ULN
  - > 8x – ≤ 10x ULN
  - > 10x – ≤ 20x ULN
  - > 20x ULN

- ALT or AST
  - ≥ 3x – ≤ 5x ULN
  - > 5x – ≤ 8x ULN
  - > 8x – ≤10x ULN
  - > 10x – ≤ 20x ULN
  - > 20x ULN

- Total bilirubin (TBL)
  - ≥ 2x – ≤ 3x ULN
  - > 3x – ≤ 5x ULN
  - > 5x ULN

- Potential Hy's Law

- ALT or AST ≥3x ULN and TBL ≥2x ULN

This table includes data of subjects where ALT and/ or AST and TBL are elevated at any time (AST or ALT ≥ 3×ULN together with TBL ≥ 2×ULN).

ALT and AST elevations are also displayed in a shift table from baseline to maximum on-treatment with the addition of the following categories:

- ≤ 1.5x ULN
- 1.5x – <3x ULN

An evaluation of drug-induced serious hepatotoxicity (eDISH) plot is also produced displaying maximum post-baseline ALT or AST and the maximum post-baseline bilirubin taken within 14 days of maximum post-baseline ALT or AST.

Key information is presented for subjects with potential Hy's Law cases.

Coagulation and CCI parameters are reported for each scheduled post-baseline visit (Including follow-up) as follows:

- The descriptive statistics are presented for observed values and change from baseline.
- CCI parameters CCI are also analysed using a linear mixed models for repeated measures (MMRM). The analysis approach will be the same as described in Section 4.2.3.4.4. CCI CCI will be analysed using an ANCOVA CCI The analysis approach will be the same as described in Section 4.2.3.4.1.

Supportive laboratory listings are provided. The following laboratory parameters are also included in chemistry listings: TSH, T4, NTproBNP, Lipase, HbA1c and PEth.

Vital Signs

The following variables are collected after the subject has rested in the seated position for at least 10 minutes:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (beats per minute)
- SpO2
- Respiratory rate
- Body temperature (°C).

Vital sign status (low, normal, high) is defined using normal ranges provided in Table 4.

Table 4 - Vital Sign Normal Ranges

Vital Sign	Outside AZ defined reference range		Treatment emergent		Abnormal, clinically significant
	lower limit if	upper limit if	decrease if	increase if	
Systolic blood pressure (mmHg)	< 90	> 140	< -20	> 20	NA
Diastolic blood pressure (mmHg)	< 60	> 90	< -10	> 10	NA
Pulse rate (bpm)	< 50	> 100	< -20	> 10	NA
Body temperature (°C)	< 36	>37.2	NA	NA	< 35.8 or > 37.5
SpO2	< 94	NA	NA	NA	NA
Respiratory Rate	< 10	> 24			NA
AZ = AstraZeneca; NA = not applicable					

For vital signs, A treatment emergent abnormality is defined as a value that, for a subject, is normal at baseline and low or high at any point post-baseline while on-treatment, as per Table 4, or they have a treatment emergent increase or decrease. Treatment emergent abnormalities are tabulated.

Vital sign parameters are summarised by treatment within cohort and for the combined cohorts at each scheduled visit and time point as applicable:

- The descriptive statistics are presented for observed values and change from baseline.
- The frequency tables present number of subjects with their vital sign status (low, normal, high)

Shift tables are presented for vital sign status (low, normal, high) from baseline to maximum and minimum post-baseline value.

Supportive vital sign listings are also provided.

Physical Examination

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment is reported as an AE unless unequivocally related to the disease under study.

Data for physical examinations are not presented in separate listings or tables.

Electrocardiogram

Electrocardiograms are performed in triplicate, with one minute between readings. The following ECG parameters are collected:

- ECG mean heart rate (beats/min)

- QRS duration (msec)
- RR interval (msec)
- PR interval (msec)
- QT interval (msec)
- QT interval corrected for heart rate using Fridericia's formula (QTcF) [msec][1]
- ECG interpretation (Normal/ Abnormal/ Borderline)
- Reason for abnormal overall ECG evaluation
- ECG clinically significant? (No/ Yes)

Normal ranges for ECG are provided in the table below:

Table 5 - Normal ECG Ranges

Parameter	Low	High
PR interval (ms)	120	220
RR interval (ms)	600 (>100bpm)	1200 (<50bpm)
HR (bpm)	<50	>100
QRS interval (ms)	70	115
QTcF interval (ms)	340	450

QTcF thresholds are presented in the table below:

Table 6 - QTcF thresholds

Criterion	Categories
Observed absolute QTcF interval value	>450 ms >480 ms >500 ms
Change from baseline in QTcF interval value	>30 ms >60 ms
Combination	Absolute value >450 ms and change from baseline >30 ms Absolute value >450 ms and change from baseline >60 ms Absolute value >480 ms and change from baseline >30 ms Absolute value >480 ms and change from baseline >60 ms Absolute value >500 ms and change from baseline >30 ms Absolute value >500 ms and change from baseline >60 ms

Average values of continuous variables and the worst ECG interpretation (Abnormal [Clinically significant, not clinically significant], borderline, normal) are used for analyses.

ECG parameters are reported for each scheduled post-baseline visit (Including follow-up) and timepoint as follows:

- The descriptive statistics are presented for observed values and change from baseline.
- The frequency table presents number and percentage of subjects with ECG parameters outside normal ranges
- For QTcF, a frequency table presents number of subjects with values exceeding thresholds for observed values, change from baseline and combination of criteria
- The frequency table present number and percentage of subjects by the interpretation of the ECG reading (normal, borderline, abnormal - clinically not significant, abnormal - clinically significant), including baseline interpretation

A shift table is also provided for the interpretation utilising the subjects baseline and last on-treatment assessment.

Supportive ECG listings cover observed values for each individual subjects.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

No sensitivity analyses are performed.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

No supplementary analyses are performed.

4.2.1.7 Subgroup Analyses

No subgroup analyses are performed.

4.2.2 Secondary Endpoint

4.2.2.1 Definition

Tertiary/Exploratory endpoints are listed in the Table 2 in Section 4.2.

4.2.2.2 Derivations

Change and percentage change are defined in Section 3.3.1.

The PK parameters of the plasma and urine concentration data for AZD2389 are derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.5 or higher (Certara).

The following PK parameters are determined according to AstraZeneca standards:

Parameter Symbol	Definition

AUClast	Area under plasma concentration-time curve from time 0 to the last quantifiable concentration.
AUC0-24	Partial area under the concentration-time curve from 0-24 post dose.
AUCinf	Area under concentration-time curve from time 0 to infinity (Day 1 only). Calculate by AUClast + Clast/λz.
AUCtau	Area under concentration-time curve in the dose interval. (Day 28 only).
Rac AUC	Accumulation ratio for AUC (Steady State AUCtau / First Dose AUCtau).
Rac Cmax	Accumulation ratio for maximum observed drug concentration.
TCP	Temporal change parameter (Steady State AUCtau / First Dose AUCinf).
Cmax	Maximum observed drug concentration.
t½λz	Terminal elimination half-life (ln 2/λz).
tmax	Time to reach peak or maximum observed concentration.
tlast	Time of last quantifiable concentration
CL/F	Apparent total body clearance (Dose/AUCinf).
Vz/F	Apparent Volume of distribution based on the terminal phase ((CL/F)/λz).
CLR	Renal clearance.
Ae(t1-t2)	Individual and cumulative amount of unchanged drug excreted into urine from time t1 to time t2.
fe(t1-t2)	Individual and cumulative percentage of dose excreted unchanged into urine from time t1 to time t2. (Ae(t1-t2)/Dose)*100 or CLR/CL*100
λz	Terminal elimination rate constant.

In addition, the following plasma diagnostic PK parameters are also determined:

Parameter Symbol	Definition
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points
AUCextr	Extrapolated area under the curve from tlast to infinity (%)

Where data allows, PK analysis is carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with approval from the AZ Clinical Pharmacology Scientist. Nominal sampling times may be used for any agreed interim PK parameter calculations.

For each PK sampling period, plasma concentrations that are non-quantifiable (NQ) from the time of CCI sampling (t=0) up to the time of the first quantifiable concentration is set to a value of zero. After this time point, NQ plasma concentrations is set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile is deemed to have terminated and therefore any further quantifiable concentrations is set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile is excluded from the PK analysis.

Cmax, and tmax are taken directly from the concentration-time profiles.

Terminal Elimination Rate Constant

The terminal elimination rate constant (lambda z [λz]) is calculated by log-linear regression of the terminal portion of the concentration time profile. The following points should be considered and, in general, should ensure a good estimate of λz:

- If there is more than one phase apparent, use only data points from the terminal phase.
- Use at least 3 measured concentrations spanning three half-lives.
- Include the last measurable concentration if possible.

- Include only observations after Cmax.

The Rsq adjusted value also shows the goodness-of-fit but takes into consideration the number of points used in the estimation. To achieve a good precision in the estimation, the Rsq adjusted value should be high, e.g., a value of >0.8 is indicative of a good correlation.

Area Under the Curve

Area under the plasma concentration vs. time curve is calculated using the trapezoidal rule. In general, the 'Linear up/Log down' calculation method is appropriate. To ensure a robust estimate of AUCinf, the extrapolation (AUCextr) should be relatively small as a percentage of the whole AUCinf (e.g., ≤20%).

Amount excreted in urine

The equation for calculating the amount excreted in the urine is:

Ae = urine volume * concentration

Where weight of urine is recorded instead of volume a specific gravity of 1 g/mL is assumed therefore 1 g of urine corresponds to 1 mL.

Renal clearance

The equation for calculating renal clearance is:

CLR = Ae(0-t) / plasma AUC(0-t)

The 0-t interval is the same for both Ae and AUC. However, if the amount excreted in the urine is quantifiable over a significantly longer time interval than the concentrations in plasma are quantifiable, AUCinf may be used in the renal clearance calculation - this should be documented in the study PK Analysis Notes.

4.2.2.3 Handling of Dropouts and Missing Data

Missing data are not imputed.

4.2.2.4 Primary Analysis of Secondary Endpoint

4.2.2.4.1 Pharmacokinetic Data Presentation

4.2.2.4.1.1 Pharmacokinetic Concentrations

All reportable PK concentrations are listed for each subject in the safety analysis set by Cohort and PK Day. For urine concentration data, urine concentration and volume/weight are listed.

Three observations > Lower Limit of Quantification (LLOQ) are required as a minimum for a plasma concentration. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

Plasma concentrations for each scheduled time-point are summarised by Cohort and PK Day using appropriate descriptive statistics. Urine concentrations are not summarized.

The following descriptive statistics are presented for plasma concentrations:

- n
- n below LLOQ
- geometric mean (gmean)
- geometric coefficient of variance (%) (gCV)
- arithmetic mean (mean)
- arithmetic standard deviation (Std Dev)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as exp(μ), where μ is the mean of the data on the natural log scale.

The gCV is calculated as 100 x sqrt[exp(s^2)-1], where s is the Std Dev of the data on the natural log scale.

Where required for plots: The gSD is calculated as exp(s), where s is the standard deviation of the data on the natural log scale. The gmean ± gSD (gmean-gSD and gmean+gSD) are calculated as exp[μ ± s].

Protocol scheduled times are used to present the PK concentration summary tables and corresponding gmean concentration-time figures.

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.

- At a time point where more than 50% (but not all) of the values are NQ, the mean, SD, gmean and gCV% are set to Not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The mean, SD, gmean, minimum, median and maximum are reported as NQ and the gCV% as NC.
- The number of values below LLOQ (n < LLOQ) are reported for each time point together with the total number of collected values (n).

4.2.2.4.1.2 Pharmacokinetic Parameters

All reportable plasma PK parameters, including individual diagnostic and λz related parameters, are listed for each subject by Cohort and PK Day separately based on safety analysis set.

All PK parameters and diagnostic parameters are summarised for AZD2389 by Cohort and PK Day using appropriate descriptive statistics based on PK analysis set.

The descriptive statistics for the PK parameters are presented as: n, arithmetic mean, SD, gmean, gCV%, median, min and max. The descriptive statistics for the diagnostic PK parameters are presented as: n, arithmetic mean, SD, median, min and max.

For tmax, λz lower and λz upper the following descriptive statistics are presented: n, median, min and max.

Cumulative amount/fraction of AZD2389 excreted in urine, renal CL are listed for each subject by cohort, PK Day and protocol-scheduled times and appropriate descriptive statistics.

4.2.2.4.1.3 Graphical Presentation of Pharmacokinetic Data

All geometric mean plots grouped by cohort are based on the PK analysis set. Individual plots by subject and combined individual plots by cohort and day are based on the Safety analysis set.

For consistency, the plasma concentration values used in the geometric mean data graphs are those given in the descriptive statistics summary table for each time point.

For gmean plasma concentration-time plots, NQ values are handled as described for the descriptive statistics; if the geometric mean is NQ, the value plotted is zero for linear plots and missing for semi-logarithmic plots. Any gmean ± gSD error bar values that are negative are truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

For individual plots, plasma concentrations which are NQ prior to the first quantifiable concentration are set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations are regarded as missing.

Data permitting, the following figures are presented as appropriate:

- Individual plasma concentration versus actual time data is graphically presented on linear and semi-logarithmic scales in the individual values of plasma concentrations versus time figure, based on the safety analysis set. For repeat dose groups, the plots overlay the single and multiple dose concentration-time profiles.
- Combined individual plasma concentration versus actual times after starting dose is plotted on both the linear and semi-logarithmic scale for all subjects in the individual plasma concentrations versus time figure, based on the safety analysis set. Within very figure, plots are grouped by cohort and day.
- Figures for the geometric mean (± gSD) concentration versus scheduled time data is plotted for all PK days on both a linear and semi logarithmic scale (no gSD presented) by cohort, for all subjects in the geometric mean (gSD) plasma trough concentration versus study day figure, based on the PK analysis set. Individual trough concentrations is plotted versus PK Day and dose group (linear scale only).
- Geometric mean of cumulative amount/fraction of dose of AZD2389 excreted in urine (± gSD) versus nominal sampling time is plotted on linear scale with both cohorts overlaid on the same figure by PK day.

4.2.2.4.1.4 Precision and Rounding of Pharmacokinetic Data

PK concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

The PK parameters are presented to 3 significant figures with the exception of:

- Cmax: Present to the same number of significant figures as received from the bioanalytical laboratory
- tmax, tlast, λz lower and λz upper: present as actual time received in the data, usually to 2 decimal places
- λzN: present as integer (no decimals)

The descriptive statistics for the PK parameters are presented to 4 significant figures with the exception of min and max which are presented to 3 significant figures and the following:

- tmax, λz lower and λz upper: present as received in the data, usually to 2 decimal places
- λzN and number of values (n): present as integer

4.2.2.4.2 Change and Percentage Change in FAP Activity

FAP activity (pM/uL/min) is derived as follows,

$$\frac{\text{FAP Concentration(pM)}_{Time60} - \text{FAP Concentration(pM)}_{Time0}}{20 * 60}$$

FAP concentrations below LLOQ are to be replaced by the LLOQ value.

FAP activity is log-transformed. Change from baseline, defined as the log-transformation of the post-baseline visit value minus the log-transformation of the baseline value, is examined using linear MMRM, visit within-subject is considered as a repeated measurement. The model is adjusted for log-transformed baseline FAP activity (Day 1, CCI CCI), treatment, visit and treatment-by-visit interaction, as appropriate.

The mean log changes in FAP activity at Days 1, 7, 14, 28, and follow-up for each cohort separately, as well as for the combined cohorts, for active treatment and placebo is estimated by MMRM.

Of the multiple measurements of FAP activity on Days 1 and 28, the trough level (at CCI CCI) measurements are used in the MMRM. MMRM model uses the spatial power structure for the variance-covariance matrix as default. In case convergence issues are encountered, the following approach for structures is adopted, in the order given: first-order autoregressive and compound symmetry. Degrees of freedom are calculated using the Satterthwaite's formula.

Results from MMRM are transformed back to the original scale and presented as geometric mean and geometric mean ratio and corresponding confidence intervals.

The point estimate and 95% CI for the Geometric Mean Ratio is converted to the percentage change as follows:

$$[(geometric\ mean\ ratio - 1)\ x\ 100].$$

Descriptive summaries showing the mean change and percentage change from baseline over time are also produced for FAP activity.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.2.7 Subgroup Analyses

Not applicable.

4.2.3 Other Endpoint

4.2.3.1 Definition

Tertiary/Exploratory endpoints are listed in the Table 2 in Section 4.2.

4.2.3.2 Derivations

Change and percentage change are defined in Section 3.3.1.

4.2.3.3 Handling of Dropouts and Missing Data

Missing data are not imputed.

4.2.3.4 Primary Analysis of Other Endpoint

4.2.3.4.1 Change and Percentage Change in CCI CCI

The analysis of covariance (ANCOVA) models are used to fit change at CCI , CCI for each cohort separately, as well as for the combined cohorts. The analysis models are adjusted for the treatment, and baseline.

The treatment effect for the endpoints is estimated by LS means and SEs with corresponding 95% CIs. The differences between active treatment and placebo groups are estimated by the difference in LS mean and SE with 95% CI and P-values.

Descriptive summaries showing the mean change and percentage change from baseline are also produced.

4.2.3.4.2 Change and Percentage Change in CCI

ANCOVA models are used to fit change at CCI , CCI for each cohort separately, as well as for the combined cohorts.

The analysis approach is as described in Section 4.2.3.4.1.

Descriptive summaries showing the mean change and percentage change from baseline are also produced.

4.2.3.4.3 Change and Percentage Change in CCI

ANCOVA models are used to fit CCI CCI for each cohort separately, as well as for the combined cohorts.

The analysis approach is as described in Section 4.2.3.4.1.

Descriptive summaries showing the mean change and percentage change from baseline are also produced.

4.2.3.4.4 Change and Percentage Change in CCI

CCI ,

CCI

CCI .

MMRM models are used to fit CCI CCI for each cohort separately, as well as for the combined cohorts.

MMRM models includes treatment, baseline, visit and treatment-by-visit interaction as fixed effects. Visit within-subject is considered as a repeated measurement. MMRM model uses the spatial power structure for the variance-covariance matrix as default. In case convergence issues are encountered, the following approach for structures is adopted, in the order given: first-order autoregressive and compound symmetry. Degrees of freedom are calculated using the Satterthwaite's formula.

The treatment effect for the endpoints is estimated by least square (LS) means and standard errors (SEs) with corresponding 95% confidence intervals (CIs). The differences between active treatment and placebo groups are estimated by the difference in LS mean and SE with 95% CI and P-values.

Descriptive summaries showing the mean change and percentage change from baseline are also produced.

4.2.3.4.5 Change and Percentage Change in CCI

ANCOVA models are used to fit CCI , CCI for each cohort separately, as well as for the combined cohorts.

The analysis approach is as described in Section 4.2.3.4.1.

Descriptive summaries (Including CCI showing the mean change and percentage change from baseline are also produced.

CCI

4.2.3.4.6 Change and Percentage Change in CCI

ANCOVA models are used to fit CCI for each cohort separately, as well as for the combined cohorts.

The analysis approach is as described in Section 4.2.3.4.1.

Descriptive summaries showing the mean change and percentage change from baseline are also produced.

CCI

4.3 Pharmacodynamic Endpoint(s)

Not applicable.

4.4 Pharmacokinetics

Pharmacokinetics endpoints and analyses are described in Section 4.2.2.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

Safety endpoints and analyses apart from exposure are described in Section 4.2.1.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Duration of exposure (in days) to the study intervention is calculated as the difference between the last dose date and the first dose date + 1.

CCI is calculated as CCI.

4.6.1.2 Presentation

Duration of exposure is summarised descriptively and presented according to the rules described in Section 3.3.

CCI is summarised descriptively and presented according to the rules described in Section 3.3.

5 INTERIM ANALYSIS

Not applicable.

6 REFERENCES

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7 APPENDIX

Not applicable.