STATISTICAL ANALYSIS PLAN

Study Code	D6581C00001
Edition Number	2
Date	29-Apr-2024

A Phase IIa, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability, and Pharmacodynamics of AZD4831 in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis (NASH) with Fibrosis

Redacted for Public Disclosure

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase/Transaminase
CCI	CCI [redacted]
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase/Transaminase
ATC	Anatomical Therapeutic Chemical
CCI	CCI [redacted]
BMI	Body Mass Index
BP	Blood Pressure
CCI	[redacted]
[redacted]	[redacted]
CI	Confidence Interval
CCI	[redacted]
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	Concomitant Medication
CV	Coefficient of Variation
COVID-19	Coronavirus Disease 2019
CS	Compound Symmetry
CSP	Clinical Study Protocol
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDV	Early Discontinuation Visit
CCI	[redacted]
[redacted]	[redacted]
FAS	Full Analysis Set

Abbreviation or Specialized Term	Definition
FDA	United States Food and Drug Administration
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
HbA1c	Hemoglobin A1c
CCI [redacted]	[redacted]
HLG	High Level Group Term
CCI [redacted]	[redacted]
[redacted]	[redacted]
IP	Investigational Product
IPD	Important Protocol Deviation
IRT/RTSM	Interactive Response Technology/Randomization and Trial Supply Management
CCI [redacted]	[redacted]
LLoQ	Lower Limit of Quantificaiton
LME	Linear Mixed Effects
CCI [redacted]	[redacted]
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dicitionary for Regulatory Activities
MI	Multiple Imputation
CCI [redacted]	[redacted]
MPO	Myeloperoxidase
MPOi	Myeloperoxidase inhibitor
NAFLD	Non-Alcoholic Fatty Liver Disease
NAS	Non-Alcoholic Fatty Liver Disease Activity Score
NASH	Non-Alcoholic Steatohepatitis
CCI [redacted]	[redacted]
[redacted]	[redacted]
CCI [redacted]	[redacted]

Abbreviation or Specialized Term	Definition
CCI	[redacted]
PD	Pharmacodynamic
PK	Pharmacokinetics
Pro-C3	released N-terminal propeptide of type III collagen
CCI	[redacted]
[redacted]	[redacted]
PROC	The PROC step consists of a group of SAS statements that call and execute a procedure
PT	Preferred Term
SAE	Serious adverse event
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
CCI	[redacted]
ULoQ	Upper Limit of Quanitfication
WHODD	World Health Organisation Drug Dicitionary

AMENDMENT HISTORY

Section	Date	Description	Description of change	In line with CSP	Rationale
Version 1					
N/A	26 Apr 2023	N/A	Initial approved SAP	N/A	N/A
Version 2					
3.3.1.3 Laboratory data principles	29 Apr 2024	Updated with how to impute missing values	Added text around imputation when "< x" or "> x"	Yes	Information missing
3.3.1.5 Imputation of missing dates	29 Apr 2024	Added: Incomplete stop dates imputation rules Incomplete adverse event dates imputation rules Death date completely missing imputation rules Incomplete efficacy dates imputation	Added imputation rules for missing IP stop date and missing death date. Incomplete rules for AE dates and efficacy dates were updated.	Yes	Information missing
4.1.2.1 Definitions and Derivations	29 Apr 2024	Added "Safety Analysis Set and Safety Set can be used interchangeably"	Added "Safety Analysis Set and Safety Set can be used interchangeably"	Yes	Clarification

4.1.8.1 Prior and Concomitant medication – Definitions and Derivations	29 Apr 2024	Changed number of days from 29 to 14	Changed number of days from 29 to 14 for text around prior and concomitant medications to harmonize with on-treatment definition	Yes	Harmonisation with on-treatment definition
4.2.1 Primary End-Point – 2 Derivations & 4 Primary Analysis of Primary Endpoint	29 Apr 2024	Removed Week 6 from definitions.	Removed Week 6 from definitions of which time-points of measurements to use for Pro-C3	Yes	Correction as no measurement was taken at week 6
4.2.4.1 Other Endpoint - Definition	29 Apr 2024	Added description on calculating BMI/weight as this is not collected at week 12.	Added “Weight is only measured at screening and at the follow-up visit. Scores including BMI/weight will for the Week 12 score value use BMI/weight from Week 16. If that is missing, instead the latest of the screening BMI/weight will be used”	Yes	Clarification
4.1.2 Analysis sets – Definition and derivations	29 Apr 2024	New definition inlcuding at least one dose of Full Analysis Set.	Added “and received at least one dose of investigational product” to definition of Full Analysis set.	No	If a subject does not receive any dose, it can be considered noise as it in practice could have been randomized to any treatment. There is no possibility for treatment to affect the outcome of the patient. This was considered at a stage when it was too late to change CSP.

3.3.1.2 Study periods	29 Apr 2024	Clarifying how to handle all cases when calculating study periods with this more extensive description.	To definition of both On-study period and On-treatment period added: "If withdrawal of consent or death did not occur, it will be calculated from the time of the first dose of IP and to the earliest of 14 days after last dose of study drug or the last study visit. If the timepoint of first dose of IP is missing, only the day of first dose of IP will be used."	Yes	Clarification
3.3.1.4 Study day & AE onset day	29 Apr 2024	Changed definition of study day calculation per analysis set.	Changed to define study days based on analysis set. First dose for analysis using safety set. Randomization for analysis using Full analysis set or all enrolled subjects.	Yes	Change to handle the unlikely event that a subject is dosed without randomization. This subject would per the old definition not have a way to calculate study day.
3.3.1.2 Study periods	29 Apr 2024	Changed defintition of pre-treatment period to include time.	Changed so that pre-treatment period ends at timepoint of first dose instead of day before first dose.	Yes	This change is done to handle the measurements done prior to first dose on first dose day. These are to be in the pre-treatment period.
3.3.1.1 Baseline	29 Apr 2024	Changed baseline definitions.	Changed baseline definitions to be described by algorithm to be used. This takes into regard both date & time.	Yes	Clarification
3.3.1.2 Study periods	29 Apr 2024	Added special case regarding orthostatic hypotension test for study periods.	Added special case regarding orthostatic hypotension test to use time regarding on-treatment/on-study period.	Yes	Clarification

4.1.2 Analysis sets	29 Apr 2024	New set definition.	Added “All enrolled set” definition	Yes	Clarification
4.2.4.3 Handling of dropouts and missing data	29 Apr 2024	Updated to not impute exploratory data.	Updated text to “Missing data will not be imputed. There will be an assumption of missing at random for the endpoints analyzed by MMRM.”	Yes	As this is exploratory the study team decided not to impute to reduce complexity.
4.2.2.4 Primary analysis of other endpoint	29 Apr 2024	Updated to not impute exploratory data.	Changed to not impute any missing values of exploratory endpoints	Yes	As this is exploratory the study team decided not to impute to reduce complexity.
4.1.1.1 Subject disposition and completion status – definitions	29 Apr 2024	Updated with definition on screen failures	Updated with definition on screen failures	Yes	Clarification
3.3.1.1 Baseline	29 Apr 2024	Baseline algorithm description.	Moved detailed description of baseline algorithm into appendix	Yes	As it is a very detailed description defining the algorithm of picking baseline, it was moved to its own appendix.

4.1.1.1 Study population – Definitions and Derivations	29 Apr 2024	Updated to not report descriptive and summary stats connected to COVID-19.	Removed the two bullets connected to COVID-19: Subjects who discontinued treatment due to global/country situation, if applicable, will be presented. Subjects who withdraw from study due to global/country situation, if applicable, will be presented.	Yes	With the study having planned First Subject In October 2022, the impact of COVID-19 is determined to be low. No summary data on study disruptions and number of subject dispositions specifically due to COVID-19 will be reported, any such disruptions or dispositions will be handled as other disruptions or dispositions. A listing of all inputs connected to a global/country/area situation will be provided in appendix.
4.1.7 Medical History and Concomitant Disease	29 Apr 2024	Updated Concomitant medication definition.	Changed the number of days for concomitant medication to not include medication with start day 15 days or more after last dose of IP	Yes	Harmonisation with on-treatment definition
3.3.1.6 General Study Level Definitions – Descriptive and Summary statistics	29 Apr 2024	Language update.	Removed defining “at the same timepoints”.	Yes	Not necessary to mention at the same timepoints as this is understood from “similarly to absolute values”.

3.3.3 Handling of Unscheduled Visits	29 Apr 2024	Removed unnecessary special case for imputing vital signs.	Removed: “In some instances, several assessments of a vital sign variable are scheduled at the same visit for different purposes, e.g., systolic blood pressure at Visit 3. In this situation, the measurement from the assessment for only vital signs purposes would be used, unless this is missing. If it is missing, then the supine BP pre-orthostatic test measurement or would be used for the analysis.”	Yes	Text no longer applicable

3.3.5.1 Covid-19	29 Apr 2024	Changed to only report listing of subjects reporting being impacted by a global/area/country-situation “	Replaced “Subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic will be listed. Subjects affected by the COVID-19 pandemic, such as efficacy and safety assessments not per CSP, will be recorded as protocol deviations. Summaries of COVID-19 study disruptions and number of subject dispositions due to COVID-19 will be presented.” With “With the study having planned First Subject In October 2022, the impact of COVID-19 is determined to be low. No summary data on study disruptions and number of subject dispositions specifically due to COVID-19 will be reported, any such disruptions or dispositions will be handled as other disruptions or dispositions. “	Yes	Standard text on COVID-19 not considered as relevant due to study starting in October 2022.
4.2 Endpoint analysis	29 Apr 2024	Added footnote that analysis of CCI will not be performed as limited data is available.	Added footnote that analysis of CCI will not be performed as limited data is available.	No	Measurements were not available as described by schedule of assessments in CSP.

4.2 Endpoint analysis	29 Apr 2024	Updated endpoints analysis list.	Updated endpoints analysis list, removed/moved/added exploratory endpoints in objectives 5-9.	Yes	These endpoints have been identified as being of scientific interest since the start of the study.
4.6.4.2 Clinical laboratory, Urinalysis	29 Apr 2024	Removed descriptive statistics for Urinalysis variables..	Removed "Absolute change from baseline will be presented for continuous variables using descriptive statistics for all scheduled assessments after baseline."	Yes	Clarification as no continues values are available.
4.2.1.4 Primary Analysis of Primary Endpoint	29 Apr 2024	Updated to use separate ANCOVA model per visit.	Updated to use separate ANCOVA model per visit. "The variable will be analyzed using a separate ANCOVA model per visit instead of the repeated measurements LME model."	Yes	Clarification
4.2.4.1 Other Endpoint	29 Apr 2024	Description of measurement to use for Weight/BMI	Updated text regarding weight measurement to "There is no planned measurement for weight during week 12 visit, there is a planned measurement at week 16. For weight/BMI, the measurement closest in time to week 12 target day will be used, including both scheduled and unscheduled measurements."	Yes	Clarification

4.6.7 Electrocardiogram	29 Apr 2024	Removed change from baseline table output for Electrocardiogram.	Removed "key subject information will be presented for subjects with treatment emergent changes." The information for specific patients are available in the listing.		There are no continuous variables, only categorical, which makes the change from baseline assessment not applicable.
Naming convention	29 Apr 2024	Changed all naming of "Other endpoint" to "Exploratory endpoint".	Changed all naming of "Other endpoint" to "Exploratory endpoint".	Yes	To align with language used in CSP
4.6.8 Other Safety Assessment – Orthostaic hypotension	29 Apr 2024	New definition of analysis visit window for orthostatic hypotension.	Added text on calculation of analysis visit window for orthostatic hypotension. "The orthostatic hypotension analysis visit window is calculated based on first-dose date. The visit windows are the same days as for other assessments."	Yes	Clarification
4.6.8.2 Other Safety Assessments - Presentation	29 Apr 2024	Updated output connected to Orthostatic hypotension-test.	Updated description of listings to be produced to "A listing of all orthostatic test results will be provided. A listing of AEs, SAEs and DAEs by SOC/PT for subjects with at least one test sequence suggestive of Orthostatic hypotension will be presented. Adverse events occurring within 3 hours after first dose of IP for the baseline visit or the 12 weeks measurement will be flagged."	Yes	Concentrated previously overlapping listings to one. Added the new listing to include all orthostatic test results to make it possible to look at each test sequence in detail.

4.6.8.2 Other Safety Assessments – Presentation	29 Apr 2024	Updated populations to output data connected to Orthostatic hypotension-test.	Updated the segment with follow: “The tables will display data for two groups: the full analysis set and the subgroup with stable supine measurements. If replicate measurements differ by no more than 10 mmHg for systolic and 5 mmHg diastolic, the supine BP will be considered stable.”	Yes	Update following discussions with patient safety as blinded information showed that many OH investigations were performed without having stable supine BP.

1 INTRODUCTION

This statistical analysis plan (SAP) is based on the three most current protocols for each region finalized on the 18th of April (the European Union), 1st of March (the United States), and 20th of March 2023 (rest of the world). This SAP serves all three protocols. The SAP includes detailed procedures for executing the final statistical analyses related to the primary, secondary, safety and explorative objectives of the study.
AZD4831 (mitiperstat) is a highly potent MPO inhibitor (MPOi) that is being developed for the management of cardiovascular and metabolic disease. AZD4831 is hypothesized to delay disease progression and potentially reverse disease in NASH with fibrosis through direct disease-modifying effects.

This Phase IIa study will evaluate the safety and pharmacodynamics of once daily of 5 mg AZD4831 in adults with biopsy-proven non-cirrhotic NASH with fibrosis stage F1, F2 or F3.

1.1 Study design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicentre Phase IIa study including approximately 90 randomized adult participants with biopsy-proven non-cirrhotic NASH with fibrosis (NAS≥ 4, fibrosis stages F1, F2, F3). The study will be conducted at approximately 48 sites across about 9 countries.

The study will be comprised of 3 periods totaling approximately 24 weeks. The study is divided into a planned screening period of up to 8 weeks followed by a treatment period of 12 weeks and ending with a follow up period of 4 weeks.

During screening, the participants will be checked for eligibility and enrolled in the study. Following the up to 8-week screening period, approximately 90 participants will be randomized at Visit 4 in a 1:1 ratio to once daily dosing of 5 mg AZD4831 or placebo.

All participants will be treated once daily with 5 mg AZD4831 or placebo for the 12 weeks of treatment. The safety, tolerability, and pharmacodynamics will be evaluated at 12 weeks.

1.2 Randomization

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM.

Eligible subjects will be randomly assigned to AZD4831 5 mg or matching placebo in a 1:1 ratio. Subjects will be treated with AZD4831 or placebo for 12 weeks.

1.3 Number of subjects

About 300 subjects are expected to be enrolled to achieve approximately 90 eligible subjects. Subjects will be randomly assigned at a 1:1 ratio to one of the 2 treatment groups listed below:

- AZD4831 5 mg
- Placebo matching dose

The sample size is driven by the objective to assess the efficacy of AZD4831 of lowering alanine aminotransferase (ALT). Accounting for missing data, the randomization scheme described above aims to ensure that there are at least 40 subjects exposed to AZD4831 for 12 weeks, and at least 40 subjects treated with matching placebo for 12 weeks, with evaluable observations of ALT both at baseline and at end of treatment. Under the assumption of a standard deviation of 0.50 for change from baseline in log-transformed ALT, 40 participants per arm would render 80% power to detect a 25% decrease in ALT levels at end of treatment relative to baseline for AZD4831 treated versus placebo treated on a one-sided test with an alpha of 5%. Missing observations will be imputed, but to account for a potential loss in the ability to capture treatment effect when including imputed data, the aim is to randomize 45 participants per arm.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Full analysis set have been changed to include patients who are randomized and have been given at least one dose.

Analysis on explorative endpoint *Oxidative damage biomarkers* are not included in CSR.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The study is divided into a screening period of up to 8 weeks, a planned treatment period of 12 weeks followed by a safety follow-up period of 4 weeks.

The final clinical lock for writing the CSR will occur once all subjects have completed their full study participation or withdrawn from study.

3.2 Analysis Populations

See Section 4.1.2 for definition of estimand populations.

3.3 General Considerations

3.3.1 General Study Level Definitions

3.3.1.1 Baseline

For Safety Analysis Set (SAS), baseline is last non-missing value prior to or on first dose date, for further details see appendix.

For analyses on the full analysis set (FAS), baseline is determined according to the same rules as for analyses on SAS, except that for subjects whose date of first dose is different from the date of randomization baseline is determined as follows:

- Baseline is defined as the last non-missing value prior to or on the date of randomization.

For both FAS & SAS, post-baseline is defined as any value after baseline value.

Further details on selecting which measurement to use as baseline value are explained in Appendix 7.1.

3.3.1.2 Study periods

Study periods for the full analysis set

Enrolment period

The enrolment period starts at the date of signed informed consent and ends at the date before randomization. For subjects enrolled but not randomized, the enrolment period ends on the date of last visit.

Planned treatment period

The follow-up time during the planned treatment period will be calculated from the date of randomization to the date of end of planned treatment period visit (Visit 8), irrespective of if the subject has discontinued IP prior to this visit.

If the end of the planned treatment period visit is missing or has occurred outside of the visit window, for the purpose of defining the planned treatment period, it will be replaced by the earliest of:

- the upper end of the visit window of the end of planned treatment period visit (Day 105),
- the date of withdrawal of consent,
- the date of death,
- the date of the last study visit,

where the date of death and withdrawal of consent will be considered a study visit in this context.

Full study period

The follow-up time for the full study period will be calculated from the date of randomization and to the earliest of date of death, withdrawal of consent or last study visit (the date of death and withdrawal of consent will be considered a study visit in this context).

Study periods on the safety analysis set

Pre-treatment period

The pre-treatment period starts at the date of signed informed consent and ends at the date before-first dose of IP.

On-study period

The follow-up time for the on-study period will be calculated from the date of first dose of IP and to the earliest of date of death, and withdrawal of consent. If withdrawal of consent or death did not occur, it will be calculated from the date of the first dose of IP and to the date of the last study visit.

On-treatment period

The follow-up time for the on-treatment period will be calculated from the date of first dose of IP and to the earliest of 14 days after last dose IP, date of death, and withdrawal of consent. If withdrawal of consent or death did not occur, it will be calculated from the date of first dose of IP and to the earliest of 14 days after last dose of study drug or the last study visit.

Orthostatic hypotension

Any AEs connected to orthostatic hypotension test will use date & time of first dose as start of on-study period & on-treatment period and consequently end of pre-treatment period.

3.3.1.3 Laboratory data principles

Assessed values of the form '<x' (below the lower limit of quantification [LLoQ]) or '>x' (above the upper limit of quantification [ULoQ]) will be imputed as 'x/sqrt(2)' for '<x' and 'x' for '>x' in the calculations of summary statistics but displayed as '<x' or '>x' in listings. The number of imputations will be summarized. Missing safety laboratory data will not be imputed.

3.3.1.4 Study day & AE onset day

Study day is calculated from randomization date. Study day 1 is the day of randomization, study day -1 is the day prior to the date of randomization, there is no study day 0.

- If the date of the event is on or after the randomization date, then:

  Study Day = date of event – date of randomization + 1 day

- If the date of the event is prior to the randomization date, then:

  Study Day = date of event – date of randomization

AE onset day is calculated from the first dose date. AE onset day 1 is the day of first dose, AE onset day -1 is the day prior to the date of first dose, there is no AE onset Day 0.

- If the date of the event is on or after the first dose date, then:

  AE onset day = date of event – date of first dose + 1 day

- If the date of the event is prior to the first dose date, then:

  AE onset day = date of event – date of first dose

AE stop day is calculated from the first dose date with the same algorithm as AE onset day.

3.3.1.5 Imputation of missing dates

The following imputed dates will only be used for analysis purposes and will remain as reported (partially or completely missing) in subject listings.

Incomplete IP stop dates

Partially missing IP stop dates will be imputed as follows:

- If the day value of last dose is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of a known administration of IP, then this date will be used.

Incomplete adverse event dates

Partially or completely missing adverse event (AE) onset dates will be imputed as follows:

- If only the day value of the adverse event onset date is missing, the first day of the month will be used; unless this occurs in the same month and year as the latest of randomisation and date of first dose of IP, then the latest of the two will be used.
- If the day and month values of the adverse event onset date are missing, January 1 will be used; unless this occurs in the same year as the latest of randomisation and date of first dose of IP, then the latest of the two will be used.
- If the adverse event onset date is completely missing, the latest of randomisation and date of first dose of IP will be used.

If the ongoing flag is missing, then it is assumed that the AE has not stopped, and the end date will not be imputed. Otherwise, partially, or completely missing AE end dates will be imputed as follows:

- If only the day value of the adverse event end date is missing, the last day of the month will be used unless month is same as month of last dose of study drug, then impute last dose date.
- If the day and month values of the adverse event end date are missing, December 31 will be used unless year is the same as last dose date, then last dose date will be used.
- If the adverse event end date is completely missing and the AE has stopped, the first dose date will be imputed if the AE start date is prior to the first dose date, and one

day after the last dose date will be imputed if the AE start date is on or after the first dose date.

Incomplete death dates

Partially or completely missing death dates will be imputed as follows:

- If only the day value of the death date is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of last visit, then the date of last visit will be used.
- If the day and month values of the death date are missing, January 1 will be used; unless this occurs in the same year as the date of last visit, then the date of last visit will be used. If the death date is completely missing, the date of last visit will be used.
- If the death date is completely missing, last visit date will be used.

Incomplete efficacy event dates

Partially or completely missing event onset dates will be imputed as follows:

- If only the day value of the event onset date is missing, the first day of the month will be used; unless this occurs in the same month and year as randomsation, then the date of randomization will be used.
- If the day and month values of the event onset date are missing, January 1 will be used; unless this occurs in the same year as randomization, then the date of randomization will be used.
- If the event onset date is completely missing, the date of randomization will be used.

Incomplete concomitant medication dates

For medications that started prior to study start, start day will not be imputed. Partially or completely missing concomitant medication (CM) start dates will be imputed as follows:

- If only the day value of the CM start date is missing, the first day of the month will be used; unless this occurs in the same month and year as the date of randomization, then the date of randomization will be used.

- If the day and month values of the CM start date are missing, January 1 will be used; unless this occurs in the same year as the date of randomization, then the date of randomization will be used.

- If the CM start date is completely missing, the date of randomization will be used.

If medication is marked as 'Treatment continues', the stop date will not be imputed. Partially or completely missing CM stop dates (where applicable) will be imputed as follows:

- If only the day value of the CM stop date is missing, the last day of the month will be used; unless this occurs in the same month and year as the last visit, then the date of the last visit will be used.

- If the day and month values of the CM stop date are missing, December 31 will be used; unless this occurs in the same year as the last visit, then the date of the last visit will be used.

- If the CM stop date is completely missing, the date of the last visit will be used.

3.3.1.6 Descriptive and summary statistics

Quantitative data will be summarized by descriptive statistics including number of subjects in category (n), mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Geometric mean and coefficient of variation (CV) will be calculated in addition to arithmetic mean and SD, if appropriate.

Categorical data will be summarized as the number and percentage of subjects in each treatment group for each category. When appropriate, the number of missing observations will be presented, and these will not be included in the denominator when calculating percentages.

A general rule is to present descriptive summary statistics (mean, SD, median, Q1, Q3) to 1 more decimal place than the individual values. The minimum and maximum values should be reported to the same number of decimal places as the individual values.

Change from baseline, including both absolute change from baseline and percent change from baseline, will be summarized by descriptive statistics similarly to absolute values, except for

at baseline. For instances where observations are non-positive, percentage change will not be reported.

All confidence intervals (CIs) will be two-sided and 95% unless stated otherwise.

3.3.1.7 Subject convention

The term “Participant” is generally used to refer to language based on the CSP, vendor technology, patient-reported outcomes, and publication titles. The word “subject” is more commonly encountered in the statistical sections of this SAP for consistency with standard statistical terminology. Participant, patient, and subject are used interchangeably.

3.3.2 Visit Window

Visit windows will be used for analyzing visit-based data and are based on the target day for a scheduled visit, see Schedule of Activities in the CSP. The range of the windows for scheduled on-site assessments are shown in Table 1.

The visit closest to the target day and within the visit window is assigned. This can be a scheduled or unscheduled assessment.

Table 1 Visit windows

Scheduled assessment	**Visit**	**Target Day**	**Visit Window [start day, end day]**
Baseline (Week 0)	Visit 4	1	-
Week 2	Visit 5	15	[12,25]
Week 4	Visit 6	29	[26,49]
Week 8	Visit 7	57	[50,77]
Week 12	Visit 8 /EDV	85	[78,105]
Week 16	Visit 9	113	[106,127]

3.3.3 Handling of Unscheduled Visits

Unscheduled visits can be assigned to a visit window if closer to the target day than the scheduled visit or if there is no measurement from a scheduled visit in the window. If a patient has performed more than one unscheduled visit within a window, the assessment closest to the target day will be used.

In case of ties between scheduled or unscheduled visits located on different sides of the target day, the earlier assessment will be used. In case of ties located on the same side of the target day (i.e., more than one value for the same day but different time), the value with the earlier entry time will be used (except Baseline Week 0 where the value with the later entry time will be used). If assessments are on the same day, at least one with time, the assessment(s) with time will be used.

In case of two or more scheduled or unscheduled visits for assessments with the same purpose and with identical dates and times (including possibly missing times), the average value will be derived, and in case that the record is assigned for its respective analysis visit, the average value will be used for analysis. This will be done both for cases with multiple baseline values or with multiple post-baseline values with the same date and time.

3.3.4 Multiplicity/Multiple Comparisons

No multiplicity adjustment will be conducted.

3.3.5 Handling of Protocol Deviations in Study Analysis

Protocol deviations are listed in Section 4.1.3. The definition and handling of important protocol deviations (IPDs) are presented in a separate Protocol Deviation Plan.

3.3.5.1 Covid 19

With the study having planned First Subject In October 2022, the impact of COVID-19 is determined to be low. No summary data on study disruptions and number of subject dispositions specifically due to COVID-19 will be reported, any such disruptions or dispositions will be handled as other disruptions or dispositions.

A listing of all inputs connected to a global/country/area situation will be provided in appendix.

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 drug compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

- Enrolled will be defined as a subject who signed the informed consent of the study.
- Randomized will be defined as a subject who has been randomized to a treatment group.
- Screen failures will be defined as participants who consented to participate in the clinical study but has not been randomized to a treatment group.
- Received treatment will be defined as a subject who has received at least one dose of IP.
- Completed treatment will be defined as a subject who has not permanently prematurely discontinued IP during study. A subject who dies during follow up without having permanently discontinued IP prior of death will be considered to have completed treatment.
- Subjects who discontinued treatment are defined as subjects who have permanently prematurely discontinued IP. The reasons for discontinuations as collected on the DOSDISC eCRF will be presented. For reason collected as other, the “specify” field will be presented in listings but not the disposition table.
- Completed study will be defined as a subject who has completed the end of planned treatment visit, or a later visit.

- Completed safety follow-up will be defined as a subject who has completed the final safety follow-up visit.

- Subjects who discontinued the study are defined as subjects who have withdrawn consent, have been lost to follow-up or died, the numbers for each of these categories will be presented.

4.1.1.2 Presentation

Subject disposition of the enrolled population will be summarized overall and, where relevant, by treatment group (number/percent of participants meeting each milestone):

- Subjects Screened including Screen failures/Subjects not randomized/Subjects not assigned

- Subjects randomized

- Subjects started treatment

- Subjects completed/discontinued treatment including reasons for discontinuation

- Subjects completed study/subjects withdrawn from study including reasons for withdrawal

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Full Analysis Set (FAS)

The FAS will consist of all subjects who were randomly assigned to study intervention and received at least one dose of investigational product. Subjects will be analyzed according to their randomized study medication assignment, irrespective of the treatment received. Participants who withdraw consent to participate in the study are included up to the date of their study termination. The FAS will be considered the primary analysis set for the primary and secondary pharmacodynamics variables as well as for the exploratory pharmacodynamics variables.

Safety Analysis Set (SAS)

The SAS consists of all subjects who have received at least one dose of investigational product. Erroneously treated subjects (e.g., those randomized to treatment A but actually given treatment B) are accounted for in the treatment group of the treatment they received. A subject who has on one or several occasions received active IP is classified as active and is accounted for in the active IP treatment group. Safety Analysis Set and Safety Set can be used interchangeably.

PK Analysis Set

The PK analysis set will consist of all participants in the FAS who have received at least one dose of AZD4831 and who have at least one valid PK sample post dose.

4.1.2.2 Presentation

The number and percentage of participants belonging to each analysis set and excluded for each possible reason will be presented in a summary table overall and by treatment group. The table will be based on the population of all enrolled participants (all enrolled set). Listings of all randomized participants excluded from the FAS population, from the safety population, and from the PK analysis population will also be provided, including reason for exclusion from the population.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations (IPDs) are defined as protocol deviations which may significantly affect the completeness, accuracy and/or reliability of the study data, or which may significantly affect a patient's right, safety or well-being. They will include (but are not limited to):

- Inclusion criteria deviations
- Exclusion criteria deviations
- 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 (IP) Deviation
- Excluded medications taken
- Deviations related to study procedure
- Other important deviation

4.1.3.2 Presentation

Important protocol deviations will be summarized and listed for the FAS by randomized treatment group and total number of subjects. The number and percentage of patients with at least one IPD category as well as the number and percentage of patients meeting each IPD category will be provided by treatment group and in total.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic based on the FAS includes:

- Age (years)
- Age group (<65, ≥65, years)
- Sex (male, female)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)

4.1.4.2 Presentation

Demographics will be presented for the FAS, by treatment group and for total number of subjects. Furthermore it will also be presented by fibrosis score and for patients with and without Type 2 Diabetes Mellitus (T2DM). Age will be presented as a continuous variable with descriptive statistics and categorically by age group. Sex, race and ethnicity will be presented as categorical variables.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline patient characteristics includes:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI Group:
    - Underweight (<18.5 kg/m^2)
    - Normal weight (≥ 18.5 kg/m^2 and <25 kg/m^2)
    - Overweight (≥ 25 kg/m^2 and <30 kg/m^2)
    - Obese (≥ 30kg/m^2)

BMI will be calculated based on weight and height of the subject at baseline.

4.1.5.2 Presentation

Baseline patient characteristics will be presented descriptively by randomized treatment group and overall and will be based on FAS. Furthermore it will also be presented by fibrosis score and for patients with and without T2DM. Height, weight and BMI will be presented as continuous variables with descriptive statistics. BMI will also be presented categorically by BMI group.

Listings

Listings of baseline patient characteristics will be presented for all subjects.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The following disease characteristics will be presented at baseline:

- History of hypertension (Yes/No)

- Neutrophil count (10^9/L)
- T2DM status (Yes/No)
- [redacted]
- Fibrosis stage (F1, F2, F3)
- ALT

4.1.6.2 **Presentation**

Disease characteristics will be presented for the FAS, by treatment group and total number of subjects. Furthermore it will also be presented by fibrosis score and for patients with and without T2DM. History of hypertension, T2DM status and fibrosis stage will be presented as categorical variables. The others will be presented as continuous variables.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Disease related medical history and surgical/procedure history will be coded according to MedDRA.

4.1.7.2 Presentation

Medical history and concomitant disease will be presented for FAS, by treatment group and in total, classified by system organ class (SOC) and preferred term (PT). Percentages will be calculated with number of subjects in FAS as denominator. Subjects with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Subjects with events in more than one SOC/PT will be counted once in each of those SOC/PT. Relevant medical and surgical/procedure history will be sorted by international order of SOC and alphabetically by PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Prior medication is defined as any medication taken by the subject before the first dose of study medication. If the end date is before or on the day of first dose of study medication, it will be defined as a prior medication.

Concomitant therapy is defined as any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) taken concurrently with study medication regardless of the start date of the medication. If a medication starts on or prior to last dose + 14 days of study medication, it is considered to be taken concomitantly. If the end date of the medication is prior to or on the day of first dose or start date of the medication is on or more than 15 days after last study medication, the medication will not be considered to be taken concomitantly.

Allowed and prohibited and/or restricted concomitant medications will be presented respectively. Section 6.5 of the CSP lists medications and treatments which are prohibited and/or restricted. All other concomitant medications are classified as allowed.

Rescue medication is considered a concomitant medication as treatment for skin reactions and will be presented separately.

All medications will be reported by ATC classification and generic drug name and are coded using the latest version of WHO Drug Dictionary (WHODD).

4.1.8.2 Presentation

Number of subjects that have taken prior and concomitant medications will be presented for FAS, by treatment group and in total, classified by ATC classification and generic drug name, and are coded using the latest version of WHO Drug Dictionary (WHODD). Percentages will be calculated with number of subjects in FAS as denominator. Subjects are only counted once per ATC classification and generic drug name regardless of the number of medications within each category. Generic drug name will be presented nested within the relevant ATC classification and sorted alphabetically by ATC classification and then generic drug name.

Prior medications, prohibited concomitant medications, allowed concomitant medications and rescue medications will be presented separately.

Listings

A listing of any concomitant medication for randomized subjects will be presented.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Compliance with study medication is defined as the number of received doses, divided by the number of expected doses, multiplied by 100, expressed as a percentage. The number of received doses is defined as the pill count difference between pills dispensed and pills returned.

The number of expected doses is defined as the number of expected doses between first dose and time of last dose according to CSP or the time when study medication is prematurely permanently discontinued. For ongoing subjects, the end date is defined to be the last returned date per drug accountability.

The level of compliance of IP per subject will be categorised as

- <80%,
- 80%-120%, and
- >120%.

4.1.9.2 Presentation

Study drug compliance for the on-study period (see section 3.3.1.2) will be derived for each subject in the Safety Analysis Set.

Study drug compliance will be presented descriptively, including mean, SD, median, Q1, Q3, minimum, maximum, and 5% and 95% percentiles and categorically by compliance group (<80%, 80%-120%, >120%). This will be presented for the SAS by treatment group and in total. The number of subjects with missing compliance will be presented.

Listings

A listing of administration and compliance of IP will be presented.

4.2 Endpoint Analyses

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

Table 2 Overview of efficacy objectives

Statistical objectives	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Primary					
Objective 1:					
To assess the effect of AZD4831 on circulating markers on hepatic injury and apoptosis or necrosis compared with placebo	Change from baseline in log-transformed ALT	FAS	Intercurrent events will be ignored (treatment policy strategy) and potential missing data will be imputed	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed ALT, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	4.2.1
Secondary					
Objective 2:					
To assess the effect of AZD4831 on circulating biomarkers of fibrosis compared with placebo	Change from baseline in log-transformed Pro-C3	FAS	Intercurrent events will be ignored (treatment policy strategy) and potential missing data will be imputed	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed Pro-C3, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	4.2.2
Objective 3:					

Statistical objectives	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
To assess the PK of AZD4831	Plasma concentration of AZD4831.	Defined in Section 4.4	Treatment policy	Descriptive Statistics	4.4
Safety					
Objective 4:					
To assess the safety and tolerability of AZD4831 as compared with placebo in participants with non-cirrhotic NASH with fibrosis.	AEs and clinical and laboratory assessments	SAS	On treatment strategy; Treatment policy strategy	Descriptive statistics	4.6
Exploratory					
Objective 5:					
To assess the effect of AZD4831 on [redacted] compared with placebo	Change from baseline at Week 12 in log-transformed: [redacted]	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed endpoints, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	4.2.4
Objective 6:					

[1] Analysis of GGT was initially planned, however with limited data available it was decided to not perform the analysis

Statistical objectives	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
To assess the effect of AZD4831 on CCI [redacted] compared with placebo	Change from baseline at Week 12 in log-transformed: • CCI [redacted]	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed endpoints, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	4.2.4
Objective 7					
To characterize the effect of AZD4831 on CCI [redacted]	Change from baseline at Week 12 in log-transformed • CCI [redacted]	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed endpoints, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	4.2.4
To characterize the effect of AZD4831 on CCI [redacted]	Change from baseline at Week 12: • CCI [redacted]	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12, where the mean is	4.2.4

Statistical objectives	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
				extracted from a linear mixed effects model	
To characterize the effect of AZD4831 on CCI	Proportion improvers, defined as a change from baseline CCI at Week 12, for population with baseline CCI	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive statistics; Shift tables describing CCI at Week CCI and Baseline. Relative risk between treatment and placebo group of having an improvement for population with CCI at baseline.	4.2.4
Objective 8					
To assess the effect of AZD4831 on CCI compared with placebo	Change from baseline at Week 12 in log-transformed: • CCI	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed endpoints, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	4.2.4
Objective 9					
To assess CCI that CCI and/or CCI	Change from baseline in log-transformed: • CCI	FAS	Intercurrent events will be ignored (treatment policy strategy)	Descriptive Statistics; Difference between AZD4831 and placebo in mean of change from baseline at Week 12 in log-transformed	4.2.4

[2] Will not be reported in CSR

Statistical objectives	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
CCI [redacted]	• CCI [redacted]			endpoints, where the mean is extracted from a linear mixed effects model, back-transformed to the original scale for presentation	

4.2.1 Primary Endpoint

4.2.1.1 Definition

The primary pharmacodynamic endpoint for this study is change from baseline to Week 12 in log-transformed ALT.

- **Treatment:** Randomized treatment group, either 5 mg AZD4831 or placebo, administered in addition to optimal background therapy for co-morbidities
- **Population:** FAS, defined through inclusion and exclusion criteria
- **Endpoint:** Change from baseline in log-transformed ALT
- **Intercurrent events:** Intercurrent events will be ignored (treatment policy strategy) and potential missing data imputed
- **Population-level summary:** Relative change versus placebo in value at end of treatment relative to baseline

4.2.1.2 Derivations

The primary analysis for the dependent variable is the change in log-transformed values of ALT, that is

$$log(ywx) - log(ybl)$$

where ywx denotes the ALT measurements at either Week 2, 4, 8 or 12 and ybl denotes the ALT at baseline.

The supplementary analysis for the dependent variable is the individual percentage change in ALT , that is

$$\frac{(ywx - ybl)}{ybl} \times 100\%$$

where ywx and ybl are the same values as above.

4.2.1.3 Handling of Dropouts and Missing Data

Any missing baseline ALT values will be imputed with the average of all non-missing baseline values of FAS participants, disregarding the treatment group. For post-baseline missing ALT values, a distinction in the imputation will be made between non-monotone and monotone missing data. Monotone missing data are defined as missing data that constitute the end of participant follow-up, while non-monotone missing data means that there are observations made after the missing time point. Any non-monotone missing data will be replaced by multiple imputations using PROC MI MCMC.

If there are sufficient retrieved dropouts per dropout-pattern by treatment group combination, monotone missing data will be imputed based on predictive mean matching imputation, otherwise placebo-washout imputation will be used. Further details can be found in Appendix 7.2. A dropout in this context is defined as a subject having stopped taking IP. They could still have non-missing values for the endpoint (= retrieved dropout).

4.2.1.4 Primary Analysis of Primary Endpoint

The null hypothesis of no decrease in ALT comparing AZD4831 to placebo will be tested versus the alternative hypothesis of a decrease in ALT in favour of AZD4831 to placebo using a one-sided test at 5% significance level. This is assessed through an estimand that uses the treatment policy strategy to handle intercurrent events and includes all participants in the full analysis set (FAS). The distribution of ALT is assumed to be well approximated by a log-normal distribution. The log-transformed endpoint will be analyzed in a linear mixed effects model (LME) with participant as random effect, treatment, visit and treatment-by-visit interaction as fixed effects, and (log-transformed) ALT at baseline as covariate. The Restricted Maximum Likelihood estimation approach will be used to fit the model.

Visit within subject will be considered as repeated measurements. The model will use an autoregressive structure for the variance-covariance matrix for unequally spaced data as

default (SP(POW)(week) in SAS). In case convergence issues are encountered, the following approach will be adopted, in the order given:

- Compound symmetry (CS) will be used instead of the autoregressive covariance structure
- The variable will be analyzed using a separate ANCOVA model per visit instead of the repeated measurements LME model.

Degrees of freedom will be calculated using the Satterthwaite's formula in case a mixed effects model is used.

Available observations at baseline, Weeks 2, 4, 8, and at the end of Week 12 will be used in the model, missing data will be imputed according to the principles outlined in section 4.2.1.3. In addition, descriptive statistics will be presented and the distribution of missing data, number and proportions, according to each missing data pattern will be summarized per treatment arm. Descriptive statistics will be based on the data collected in the study (i.e. not be based on imputed data).

Log-transformed data will be used for the analysis, and the mean difference versus baseline at all the above timepoints will be back-transformed to describe ratio to baseline in terms of geometric means and, furthermore, to describe percent change versus baseline within group and percent change versus placebo in ratio to baseline for the 5mg group.

Presentation

Least square mean estimates will be back transformed for each treatment group and each timepoint, representing least square geometric mean estimates.

For each timepoint and each treatment group, estimates for ratio of geometric mean at the timepoint versus at baseline will be presented, together with two-sided 95% CI. In addition, for each timepoint estimates for percent change from baseline within group, and percent change versus placebo including 95% CI will be presented. For the latter comparison one-sided p-values will be presented.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

The following sensitivity analyses will be conducted:

- The same approach as in Section 4.2.1.4 for the primary analysis but without imputing missing data

- Change from baseline in log-transformed ALT using a separate ANCOVA per timepoint as estimator, with imputation. The results will be back-transformed as for the primary analysis

- Change from baseline in log-transformed ALT using a separate ANCOVA per timepoint as estimator but without imputation. The results will be back-transformed as for the primary analysis

- The same approach as in Section 4.2.1.4 for the primary analysis with the extra inclusion of T2DM as a fixed factor, with imputation

- The same approach as in Section 4.2.1.4 for the primary analysis with the extra inclusion of T2DM as a fixed factor, without imputation

- The same approach as in Section 4.2.1.4 for the primary analysis with the extra inclusion of Fibrosis score as a fixed factor, with imputation

- The same approach as in Section 4.2.1.4 for the primary analysis with the extra inclusion of Fibrosis score as a fixed factor, without imputation

4.2.1.6 Supplementary Analyses of the Primary Endpoint

The supplementary analysis will be evaluated under a different supplementary estimand.

- **Treatment:** Same as the primary analysis

- **Population:** Same as the primary analysis

- **Endpoint:** Individual percentage change from baseline in ALT

- **Intercurrent events:** Same as the primary analysis

- **Population-level summary:** Difference in mean percentage values between the treatment groups

The null hypothesis of no differences in individual percent changes between AZD4831 and placebo will be tested versus the alternative hypothesis of a higher mean of individual percentage reduction in ALT in favour of AZD4831 to placebo using a one-sided test at 5% significance level, assessed through an estimand that uses the treatment policy strategy to handle intercurrent events. The endpoint will be analyzed in a linear mixed effects model with participant as random effect, treatment, visit and treatment-by-visit interaction as fixed effects, and ALT at baseline as covariate. Missing values will use the same imputation as described in Section 4.2.1.3. The covariance structure will be the same as described in Section 4.2.1.4

4.2.1.7 Subgroup Analyses

A subgroup analysis will be conducted for ALT change from baseline at 12 weeks under the primary estimand defined in Section 4.2.1.1. For the subgroup analysis the measurements collected at baseline and Week 12 will be included. For each of the pre-specified subgroup variables, a separate ANCOVA will be fitted with treatment, subgroup and subgroup-by-treatment interaction as fixed effects, and (log-transformed) ALT at baseline as covariate. The number of subjects with missing subgroup variable values is expected to be minimal, and values for these variables will not be imputed. Hence, subjects with missing subgroup values will be excluded before analyzing the corresponding variable. In case of convergence issues, separate ANCOVA models will be fitted for each subgroup.

Subgroups

The subgroup analyses will be performed for the following baseline and demographic variables

- BMI Group:
    - Underweight (<18.5 kg/m2)
    - Normal weight (≥ 18.5 kg/m2 and <25 kg/m2)
    - Overweight (≥ 25 kg/m2 and <30 kg/m2)
    - Obese (≥ 30kg/m2)
- Age group (<65, ≥65, years)

- Sex (male , female)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Fibrosis score (F1, F2, F3)
- T2DM (Yes/No)

Presentation

For each subgroup variable, least square mean estimates will be back transformed for each treatment group, each subgroup and each timepoint, representing least square geometric mean estimates.

For each treatment group and each subgroup, estimates for ratio of geometric mean at Week 12 versus at baseline will be presented, together with two-sided 95% CI. In addition, estimate for percent change versus placebo in above geometric mean ratio together with 95% CI will also be presented together with the p-value for the subgroup-by-treatment. If separate ANCOVA analyses were performed for each subgroup, no p-value will be presented.

4.2.2 Secondary Endpoint

This section concerns analysis of Pro-C3. Analysis of pharmacokinetics is described in Section 4.4.

4.2.2.1 Definition

The primary pharmacodynamic endpoint for this study is change from baseline to Week 12 in log-transformed Pro-C3.

- **Treatment**: Randomized treatment group, either 5 mg AZD4831 or placebo, administered in addition to optimal background therapy for co-morbidities
- **Population**: FAS, defined through inclusion and exclusion criteria
- **Endpoint**: Change from baseline in log-transformed Pro-C3

- **Intercurrent events:** Intercurrent events will be ignored (treatment policy strategy) and potential missing data imputed

- **Population-level summary**: Relative change versus placebo in value at end of treatment relative to baseline

4.2.2.2 Derivations

The primary analysis for the dependent variable is the change in log-transformed values of Pro-C3, that is

$$log(ywx) - log(ybl)$$

where ywx denotes the Pro-C3 measurements at either Week 4 or 12 and ybl denotes the Pro-C3 at baseline.

The supplementary analysis for the dependent variable is the individual percentage change in Pro-C3, that is

$$\frac{(ywx - ybl)}{ybl} \times 100\%$$

where ywx and ybl denote the same values as before.

4.2.2.3 Handling of Dropouts and Missing Data

Missing Data will be handled in the same way as described in 4.2.1.3.

4.2.2.4 Primary Analysis of Secondary Endpoint

The primary analysis of the secondary endpoint will be using a linear mixed effects model with participant as random effect, treatment, visit, and treatment-by-visit interaction as fixed effects, and (log-transformed) baseline as covariate, including all participants in the full analysis set (FAS). Data will be log-transformed before analyses, and results will be back transformed to describe relative change versus placebo in value at end of treatment relative to baseline.

Available observations at baseline, Week 4, and Week 12 will be used in the model, missing data will be imputed according to the principles outlined in Section 4.2.2.3. In addition, descriptive statistics will be presented and the distribution of missing data, number and proportions, according to each missing data pattern will be summarized per treatment arm.

Least square mean estimates will be back transformed for each treatment group and each timepoint, representing least square geometric mean estimates.

For each timepoint and each treatment group, estimates for ratio of geometric mean at the timepoint versus at baseline will be presented, together with two-sided 95% CI. In addition, for each timepoint estimates for percent change versus placebo in above geometric mean ratio together with 95% CI will also be presented. For the latter comparison one-sided p-values will be presented.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

The following sensitivity analyses will be conducted:

- The same approach as in Section 4.2.2.4 for the primary analysis but without imputing missing data
- Change from baseline in log-transformed Pro-C3 using a separate ANCOVA per timepoint as estimator, with imputation. The results will be back-transformed as for the primary analysis
- Change from baseline in log-transformed Pro-C3 using a separate ANCOVA per timepoint as estimator, but without imputation. The results will be back-transformed as for the primary analysis
- The same approach as in Section 4.2.2.4 for the primary analysis with the extra inclusion of T2DM as a fixed factor, with imputation.
- The same approach as in Section 4.2.2.4 for the primary analysis with the extra inclusion of T2DM as a fixed factor, without imputation.
- The same approach as in Section 4.2.2.4 for the primary analysis with the extra inclusion of Fibrosis score as a fixed factor, with imputation
- The same approach as in Section 4.2.2.4 for the primary analysis with the extra inclusion of Fibrosis score as a fixed factor, without imputation

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

The supplementary analysis will be evaluated under a different supplementary estimand.

- **Treatment:** Same as the primary analysis
- **Population:** Same as the primary analysis
- **Endpoint:** Individual percentage change from baseline in Pro-C3
- **Intercurrent events:** Same as the primary analysis
- **Population-level summary:** Difference in mean percentage values between the treatment groups

The null hypothesis of no differences in individual percent changes between AZD4831 and placebo will be tested versus the alternative hypothesis of a higher individual percentage reduction in Pro-C3 in favour of AZD4831 to placebo using a one-sided test at 5% significance level, assessed through an estimand using the treatment policy strategy for intercurrent events. The endpoint will be analyzed in a linear mixed effects model with participant as random effect, treatment, visit and treatment-by-visit interaction as fixed effects, Pro-C3 at baseline as covariate. The covariance structure will be the same as described in Section 4.2.1.4

4.2.2.7 Subgroup Analyses

A subgroup analysis will be conducted for Pro-C3 change from baseline at 12 weeks under the primary estimand defined in Section 4.2.2.1. For the subgroup analysis the measurements collected at baseline and Week 12 will be included. For each of the pre-specified subgroup variables, a separate ANCOVA will be fitted with treatment, subgroup and subgroup-by-treatment interaction as fixed effects, and (log-transformed) Pro-C3 at baseline as covariate. The number of subjects with missing subgroup variable values is expected to be minimal, and values for these variables will not be imputed. Hence, subjects with missing subgroup values will be excluded before analyzing the corresponding variable. In case of convergence issues, separate ANCOVA models will be fitted for each subgroup.

Subgroups

The subgroup analyses will be performed for the following baseline and demographic variables

- BMI Group:

- Underweight (<18.5 kg/m2)
- Normal weight (≥ 18.5 kg/m2 and <25 kg/m2)
- Overweight (≥ 25 kg/m2 and <30 kg/m2)
- Obese (≥ 30kg/m2)

- Age group (<65, ≥65, years)
- Sex (male , female)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, Asian, White, Other)
- Ethnicity (Hispanic/Latino, not Hispanic/Latino)
- Fibrosis score (F1, F2, F3)
- T2DM (Yes/No)

Presentation

For each subgroup variable, least square mean estimates will be back transformed for each treatment group, each subgroup and each timepoint, representing least square geometric mean estimates.

For each treatment group and each subgroup, estimates for ratio of geometric mean at Week 12 versus at baseline will be presented, together with two-sided 95% CI. In addition, estimate for percent change versus placebo in above geometric mean ratio together with 95% CI will also be presented together with the p-value for the subgroup-by-treatment. If separate ANCOVA analyses were performed for each subgroup, no p-value will be presented.

4.2.3 General considerations for primary and secondary endpoints

All pharmacodynamics data collected will be listed for each participant and summarized descriptively (including, but not limited to, mean, SD, minimum, median, maximum, geometric mean, geometric coefficient of variation) by treatment and time point/visit. Figures

of the mean response (absolute change from baseline, and value relative to baseline) will be used to visualize the average response over time.

4.2.4 Exploratory Endpoints

4.2.4.1 Definition

[redacted]

- CCI
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.4.2 CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

4.2.4.6 Additional Analyses of Exploratory Endpoints

No additional analyses will be performed.

4.2.4.7 Subgroup Analyses

No subgroup analyses will be performed.

4.3 Pharmacodynamic Endpoint(s)

Not Applicable

4.4 Pharmacokinetics

Plasma concentrations of AZD4831 will be summarized by timepoints and presented in the CSR. If PK data permit, a population PK model may be developed, possibly with the support of PK data from other studies, using nonlinear mixed effects regression analysis in the NONMEM program. Furthermore, if data allows, the population PK model may be coupled with separate pharmacodynamics models. All PK/pharmacodynamics modelling will be described in a separate data analysis plan. Moreover, the derived PK parameters and the results of any such modelling will be provided in a separate PK and population PK/pharmacodynamics report (as an appendix to the CSR or as a stand-alone report).

- **Treatment:** Actual treatment group (i.e., not necessarily the treatment a subject was randomized to), AZD4831 5mg
- **Population:** Patients from PK analysis set that follows their assigned dosing schedule. Patients who stop their dosing prematurely are therefore only included up to the point where they stopped dosing.
- **Endpoint:** Plasma concentrations of AZD4831
- **Intercurrent events:** Treatment policy
- **Population-level summary:** Descriptive Statistics

4.5 Immunogenicity

Not Applicable

4.6 Safety Analyses

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

Tables, figures, and listings are provided for SAS unless otherwise stated. All tabulations of safety data (AEs, laboratory parameters, vital signs, and ECG) will be based on both the on-treatment period and on-study period respectively unless otherwise stated.

Table 3. Overview of safety objectives

Statistical objectives	Endpoint	Population	Inter-current event strategy	Population level summary	Details in section
Primary Safety objectives					
Objective 1:					
To assess the safety and tolerability of AZD4831 as compared with placebo in participants with non-cirrhotic NASH with fibrosis.	AEs and clinical and laboratory assessments	SAS	While on treatment strategy; Treatment policy strategy	Descriptive statistics	4.6

- **Treatment** Actual treatment group (i.e., not necessarily the treatment a subject was randomized to), AZD4831 5mg or placebo administered in addition to optimal background therapy for co-morbidities
- **Population:** Safety Analysis Set
- **Endpoint:** AEs and clinical laboratory assessments
- **Intercurrent events:** Premature study treatment discontinuation: All analyses will be provided using two complementary strategies:
    - While on treatment strategy: Uses all available data collected during the on-treatment analysis period, defined in section 3.3.1.2
    - Treatment policy strategy: Ignoring study treatment discontinuation, implemented by including all available data, using the on-study analysis period defined in section 3.3.1.2
- **Population-level summary:** Descriptive Statistics

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Duration of exposure (days) to study drug will be calculated for each subject as

Duration of exposure (days) = date of last dose - date of first dose +1

Dose interruptions will not be taken into consideration for calculation of duration of exposure.

Total time of exposure (subjects-years) is calculated as

Total time of exposure = sum(duration of exposure for each subject) ÷ 365.25

4.6.1.2 Presentation

Duration of exposure and Total time of exposure will be presented.

Total exposure will be presented categorically by cumulative categories by every 28th day from day 1 to day 85. These categories are cumulative, and subjects will be included in all categories that apply to them.

In addition, a figure of exposure over time will be presented, and percentage of subjects still exposed on the y-axis and time from first dose on the x-axis. At a given time t, the curve will show the percentage of subjects with exposure time > t.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Each adverse event will be assigned to the on-treatment period and/or on-study period, as defined in Section 3.3.1.2. Adverse events will be classified by SOC and PT and coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released at the time of database lock.

Any AE

Defined as an AE reported with an onset date within the defined period.

Any SAE

Defined as an AE reported as serious irrespective of outcome.

SAEs with outcome death

Defined as an AE with reported outcome as 'Fatal', there may be more than one AE with outcome death for a subject. The onset date of the AE determines the analysis period, irrespective of date of death.

AEs leading to discontinuation of IP

Defined as an AE with action taken IP reported as drug permanently discontinued. The onset date of the AE determines the analysis period irrespective of date of discontinuation of IP.

AEs possibly related to IP

Defined as an AE that is reported as "reasonable possible AE caused by IP". If this evaluation is missing, it will be counted as an AE possible related to IP.

AEs by maximum intensity

AEs will be classified by the reported maximum intensity, "Mild", "Moderate" and "Severe". If this maximum intensity is missing, it will be classified as "Severe".

Adverse events of special interest

The following two groups of adverse events are Adverse events of special interest (AEoSI):

- Infections: will be identified by the SOC "Infections and infestations".
    - The pathogen-specific High level group term (HLGT) "Fungal infections disorders".
- Skin reactions, including maculopapular rash:
    - Skin reactions/rashes considered maculopapular (described as macules/papules under the morphology/appearance question).
    - Skin reactions/rashes not considered maculopapular (not described as macules/papules under the morphology/appearance question).

4.6.2.2 Presentation

Adverse events will be presented for each treatment group by System Organ Class and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview AE table will be presented for each treatment group including number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

Separate AE tables will be provided taking into consideration seriousness, death, and events leading to discontinuation of IP. An additional table will present number and percentage of participants with most common AEs, where most common is defined as more than 5% per treatment group.

In accordance with the requirements of the FDA, a separate table will present nonserious AEs occurring in more than 5% of participants in any treatment group. Key participant information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP. An AE listing for the safety analysis set will cover details for each individual AE. Adverse events of special interest related to skin reactions, including maculopapular rash, and infection will be presented.

For the summary of AEs by PT and maximum intensity, if a patient has multiple events occurring in same PT within a treatment phase, then the event with the highest intensity will be counted. For the summary of AEs by PT and investigator's causality assessment, if a patient has multiple events occurring in same PT within a treatment phase, then the event with the maximum reported causality will be counted.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for determination of clinical chemistry and haematology will be collected according to the schedule of activities in Section 1.3 of the CSP. Clinical Safety Laboratory Assessments are listed in Section 8.2.5 of the CSP.

4.6.3.2 Presentations

Clinical laboratory parameters will be presented for SAS by treatment group, and scheduled visit, separately for haematology and chemistry parameters, and the parameters will be presented in alphabetical order.

Values and absolute change from baseline will be presented for continuous variables using descriptive statistics for all scheduled assessments after baseline.

Maximum on-treatment/on-study ALT and AST versus maximum on-treatment/on-study total bilirubin will be presented by treatment group.

Shift tables will be presented for all subjects by treatment.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Clinical laboratory parameters for urinalysis will be presented for SAS by treatment group, and the parameters will be presented in alphabetical order.

Change from baseline to maximum and minimum assessment on-treatment and on-study respectively will be presented in shift tables.

Urinalysis will be taken according to the schedule of activities in section 1.3 in the CSP.

4.6.4.2 Presentation

Clinical laboratory parameters for urinalysis will be presented for the safety analysis set by the treatment group and scheduled visit. All parameters will be presented with descriptive statistics for all visits for which an assessment is scheduled.

4.6.5 Other Laboratory Evaluations

Not Applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs (supine BP [average of 3 measurements], pulse rate, height, weight, and body temperature) will be performed at the time points specified in the Schedule of Assessments in the CSP.

4.6.6.2 Presentations

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, min, Q1, median, Q3, and max. For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Listings

Listings of vital signs will be presented for all patients

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Electrocardiograms will be performed and measured as specified in the CSP.

ECG treatment emergent changes are defined as subjects with abnormal clinically significant results on-treatment that were not present at baseline.

4.6.7.2 Presentations

Summary statistics will be shown for the following categories for the Safety Analysis Set by treatment group:

- Heart rhythm category
- Overall ECG evaluation
- Was the ECG clinically significant?

Shifts from baseline to last observation on-treatment in ECG overall evaluation will be analyzed in terms of normality and clinical significance.

Treatment emergent changes

The number and percentage of subjects with ECG treatment emergent changes will be presented by treatment group for SAS, where the percentage is based on number of subjects per treatment group with a baseline value and at least one post-baseline value on treatment.

Listings

A listing for all subjects will present date of ECG performance, categories listed above and reasons if conduction was abnormal.

Electrocardiogram evaluation will be summarized and presented by treatment group for baseline and for each scheduled post-baseline assessment.

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Orthostatic blood pressure test

Orthostatic hypotension related measures are derived from the orthostatic BP measurements. The orthostatic hypotension test is described in Section 8.2.3.1 in the CSP. The following definitions will be applied:

- BP decrease: a decrease ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure.
- BP decrease reported as AE: a BP decrease and a reported AE of Orthostatic Hypotension the same day post-first dose or within the same day of the at 12 weeks measurement.
- Symptomatic BP decrease: BP decrease which the investigator judges that there were symptoms that were related to the orthostatic blood pressure measurement.
- Asymptomatic BP decrease: BP decrease which the investigator judges that there were no symptoms that were related to the orthostatic blood pressure measurement.

These categories will be presented at three timepoints:

- Post-first dose irrespective of baseline status,
- only post-first dose (including only subjects with no observed BP decrease pre-first dose), and
- at 12 weeks.

Orthostatic hypotension visit window

The orthostatic hypotension analysis visit window is calculated based on first-dose date. The visit windows are the same days from baseline (, first-dose date for orthostatic hypotension,) as for other assessments.

4.6.8.2 Presentations

Orthostatic blood pressure test

Measurements related to the Orthostatic hypotension test will be summarized for each of the three timepoints described in Section 4.6.8.1 by number and percentage of subjects with an event and total number of events based on the safety analysis set, by treatment group.

The tables will display data for two groups: the full analysis set and the subgroup with stable supine measurements.

If replicate measurements differ by no more than 10 mmHg for systolic and 5 mmHg diastolic, respectively, the supine BP will be considered stable.

Listings

A listing of all orthostatic test results will be provided.

A listing of AEs, SAEs and DAEs by SOC/PT for subjects with at least one test sequence suggestive of Orthostatic hypotension will be presented. Adverse events occurring within 3 hours after first dose of IP for the baseline visit or the 12 weeks measurement will be flagged.

5 INTERIM ANALYSIS

Not Applicable.

6 REFERENCES

Not Applicable.

7 APPENDIX

7.1 Baseline definitions

If there are multiple measurement on the same date, the algorithm below decides which measurement to use as baseline.

For analyses on the safety analysis set (SAS), baseline is determined as follows:

- If there is at least one non-missing value collected on the date of first dose and prior to the time of first dose, then baseline is defined as the last non-missing value prior to the time of first dose on the date of first dose.
- Else if there is at least one non-missing value collected on the date of first dose and with missing time, then baseline is defined as the non-missing value with missing time on the date of first dose.
- Else if the only values collected on the date of first dose are on or after the time of first dose, then baseline is defined as the first non-missing value on or after the time of first dose on the date of first dose.

- Else if there are no non-missing values collected on the date of first dose, then baseline is defined as the last non-missing value prior to the date of first dose.
  Note: if multiple non-missing values collected on the same date qualify for baseline and include both records with missing time and records with non-missing time, then the records with missing time will not be considered as eligible to be used as baseline.

If after performing the above steps there are still multiple non-missing values equally eligible to be used as baseline, then baseline is defined as an average of the tied quantitative values or as the clinically best value among the tied qualitative values.

7.2 Imputations

For cases when baseline ALT/Pro-C3 values are missing, the (log transformed) baseline values will be imputed by the average value of (log-transformed) baseline for all non-missing. For post-baseline missing ALT/Pro-C3 values, a distinction in the imputation will be made between non-monotone and monotone missing data. Monotone missing data are defined on a subject level as missing data that constitutes the end of subject follow-up, while non-monotone missing data means that observations exist after the time point with the missing data. The steps of the imputation algorithm are described in Table 1.

There are some preparations of the datasets needed prior to starting with the imputations. Each subject must have a record for all measurements indicated by the protocol; for visits where a subject did not attend or did not get a measurement, a record with the value "." must be included into the dataset. Furthermore, indicators for last visit on treatment, and whether the subject had treatment through the whole intended treatment period of 12 weeks must also be included.

Table 1 Missing data imputation algorithm, including analysis

Step		Description
1	Impute missing baseline	For all missing (log-transformed) baseline values, impute with the average of all non-missing (log-transformed) baseline values in the FAS population.
2	Impute non-monotone missing data	Impute all non-monotone missing data using the Markov Chain Monte Carlo (MCMC) method assuming missing data are CCI [redacted]. This is performed using PROC MI in SAS, stratified by CCI [redacted], with the

		CCI and CCI options in the MCMC statement. CCI will be generated using the seed 35273, CCI The imputation model will include CCI assessments CCI .
3	Impute monotone missing data	For each of the CCI imputed datasets, impute all monotone missing ALT (Pro-C3) data CCI The CCI model imputation with a CCI will be performed CCI with the seed 99463734. The statement is CCI Subjects who had missing data CCI The CCI imputation will be conducted following a process CCI This will involve CCI The process will utilize the seed 101010. Please note that the term CCI will need to be adjusted to reflect CCI in the dataset.
4	Analyse	Fit the pre-specified LME model with variance-covariance matrix structure set to SP(POW)(week) to each imputed

		dataset, all without any missing data, using CCI If not all CCI models converge, follow the approach given in section 4.2.1.4. Store the CCI resulting least square mean estimates for each treatment group and the difference between treatment groups, and the corresponding standard errors for each model.
5	Pool model estimates	Pool results using CCI in SAS by visit to provide the final least square mean estimates and 95% CIs in log scale, together with p-value for the two-sided test for difference between treatment groups. Estimates will be transformed back to the original scale (to describe ratio to baseline in terms of geometric means and, furthermore, to describe percent change versus baseline within group and percent change versus placebo in ratio to baseline for the 5mg group compared to placebo). CCI