STATISTICAL ANALYSIS PLAN	
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A Phase II Randomized, Double-blind, Placebo-controlled, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Cotadutide in Participants with Non-cirrhotic Non-alcoholic Steatohepatitis with Fibrosis

Statistical Analysis Plan

Part A

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
APRI	AST-to-Platelet Ratio Index
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BARD	BMI, AST/ALT Ratio, Diabetes
BMI	Body Mass Index
CAP	Percentage-Controlled Attenuation Parameter
CM	Concomitant Medication
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CMH	Cochran-Mantel-Haenszel
CV	Cardiovascular
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
FAS	Full Analysis Set
FAST	FibroScan-ALT
FIB-4	Fibrosis-4
FPG	Fasting Plasma Glucose
GGT	Gamma Glutamyl Transferase
GLP-1	Glucagon-Like Peptide-1
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
INR	International Normalized Ratio

Abbreviation or Specialized Term	Definition
IP	Investigational Product
IPD	Important Protocol Deviation
IRT/RTSM	Interactive Response Technology/Randomization and Trial Supply Management
LCL	Lower Confidence Limit
LDL	Low-Density Lipoprotein
LLOQ	Lower Limit of Quantification
LSM	Liver Stiffness Measurement
LSMEAN	Least Squares Mean
LSMD	Least Squares Mean Difference
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MMRM	Mixed Model for Repeated Measures
NAS	Non-Alcoholic Fatty Liver Disease Activity Score
NASH	Non-Alcoholic Steatohepatitis
NFS	Non-Alcoholic Fatty Liver Disease Fibrosis Score
PK	Pharmacokinetics
PP	Per protocol
Pro-C3	Released N-terminal propeptide of type III collagen
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT-2	Sodium-glucose Transport Protein 2
SI	International System of Units
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TBL	Total Bilirubin
UCL	Upper Confidence Limit
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	11FEB2022	Initial approved SAP	N/A	N/A
Timing of Analysis	10NOV2022	3.1 Interim analysis of Part A data has been removed. Analysis will occur after DBL for Part A data. Results may be shared internally/externally prior to completion of Part B.	Yes	Align with CSP amendment
Safety Analysis	10NOV2022	3.2, 4.5 Participants receiving the wrong treatment will be analyzed according to the majority treatment received.	Yes	Align with CSP amendment
Estimand	10NOV2022	3.3, 4.2, and throughout document. The strategy for the primary estimand of histology endpoints was clarified to be a hybrid of the treatment policy and composite strategies.	Yes	Align with CSP amendment
Imputation of Missing Dates	10NOV2022	3.3.1.5.2, 3.3.1.5.3 Rules for imputation of AE start dates and CM end dates, if completely missing, were added.	Yes	Alignment with internal statistical guidance
Analysis Visit Windows	10NOV2022	3.3.2 Analysis visit window for Part B shortened to ± 90 days.	Yes	More closely align to target estimand and reduce risk for imbalance in biopsy timing
Analysis Visit Windows	10NOV2022	3.3.2 Analysis visit windows for Part A 36-week extension period removed.	Yes	Align with CSP amendment
Analysis Visit Windows	10NOV2022	3.3.2 Fasting labs not collected under a fasting condition will be excluded from analysis. If a lab is incorrectly not collected under fasting condition and repeated within the analysis visit window, the result collected under fasting condition will be preferentially used for analysis.	Yes	Clarification
Multiplicity	10NOV2022	3.3.4 Multiplicity strategy for Part B was changed.	Yes	Align with CSP amendment

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Protocol Deviations	10NOV2022	3.3.5 Text updated to refer to the Protocol Deviation (PD) Plan for full list of important protocol deviations.	Yes	Correction
General	10NOV2022	4.1.7.1, 4.5.2.1 MedDRA version was updated.	Yes	New version to reference
General	10NOV2022	4.1.8.1 WHO Drug Dictionary version was updated.	Yes	New version to reference
Efficacy Analysis	10NOV2022	4.2 Removed duplicate supplementary analysis "Hypothetical strategy – only including participants with **post-baseline biopsy** at Week 48. No imputation."	Yes	Correction
Efficacy Analysis	10NOV2022	4.2 The described estimand for complete-case analysis was updated (no change in planned analysis).	Yes	Clarification
Efficacy Analysis	10NOV2022	4.2.1.2 Derivation of primary endpoints from histopathology data transfers specified. Derivation of composite variables (considering liver outcomes) added.	Yes	Clarification and update for change in intercurrent event strategy
Efficacy Analysis	10NOV2022	4.2.1.3 Updated language regarding collection of biopsies in the event of treatment discontinuation.	Yes	Align with CSP amendment
Efficacy Analysis	10NOV2022	4.2.1.4 Updated to indicate the analysis variable is a composite of the histology result and liver outcome.	Yes	Consistency with updates to the primary estimand
Efficacy Analysis	10NOV2022	4.2.1.5 For multiple imputation analyses of biopsy endpoints, missing biopsy data will not be imputed if there is a liver outcome but per hybrid estimand will be considered a treatment failure. The imputation model will be fit using only participants without a liver outcome.	Yes	Clarification
Efficacy Analysis	10NOV2022	4.2.1.5, 4.2.1.6 Complete-case analysis, now reclassified as a sensitivity analysis, was moved	Yes	Consistency

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
		accordingly to the section describing sensitivity analyses.		
Efficacy Analysis	10NOV2022	4.2.1.6, 4.2.1.3, 4.2.2.3 Complete-case analyses will only include results from biopsies collected within the analysis visit windows.	Yes	Clarification
Efficacy Analysis	10NOV2022	4.2.1.7 Corrected a formatting issue with the list of subgroups.	Yes	Formatting
Efficacy Analysis	10NOV2022	4.2.2.3, 4.2.2.4, 4.2.3.3 Primary analysis of progression to cirrhosis will use multiple imputation (placebo washout).	Yes	Discussions with FDA
Efficacy Analysis	10NOV2022	4.2.2.7 Subgroup analysis by fibrosis stage added for progression to cirrhosis.	Yes	Additional analysis
Efficacy Analysis	10NOV2022	4.2.3.1 List of exploratory endpoints updated.	Yes	Align with CSP amendment
Safety Analysis	10NOV2022	4.5 The potential to include statistical contrast measures for safety data (such as risk difference) was introduced.	Yes	Clarification
Safety Analysis	10NOV2022	4.5 For Part B, clarified that all described safety analyses will be performed using the full treatment period (84 weeks + extension), while additional analysis using the 84-week treatment period will be performed when appropriate.	Yes	Clarification
Safety Analysis	10NOV2022	4.5.1.1 Analysis of “actual exposure”, which was included in addition to “exposure”, was removed.	Yes	Remove redundancy
Safety Analysis	10NOV2022	4.5.2.1 Gallbladder-related disease added to list of AESIs.	Yes	Align with CSP amendment
Safety Analysis	10NOV2022	4.5.2.1 Definition of MACE added.	Yes	Clarification
Safety Analysis	10NOV2022	4.5.2.2 Description of analysis of adjudicated events added.	Yes	Clarification
Safety Analysis	10NOV2022	4.5.3.1 Specified laboratory parameters to be presented in conventional as well as SI units.	Yes	Clarification

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Safety Analysis	10NOV2022	4.5.3.1 Updated list of safety laboratory variables to remove screening labs that will not be included in CSR analyses.	Yes	Clarification
Safety Analysis	10NOV2022	4.5.3.1 Lab results below the lower limit of quantitation will be imputed as 0.99*LLOQ rather than LLOQ, and results above the upper limit will be imputed as 1.01*ULOQ instead of ULOQ.	Yes	Update made based on issues encountered for other studies
Safety Analysis	10NOV2022	4.5.3.1, 4.5.3.2 AST, ALT, and TBL shift tables were replaced with an analysis more closely aligned with the potential hepatocellular DILI algorithm described in the CSP.	Yes	More closely align analysis with CSP
Safety Analysis	10NOV2022	4.5.3.2 eDISH plots will use maximum of ALT or AST rather than maximum of ALT. In addition, cholestatic DILI screening plots were added (TBL vs ALP).	Yes	Clarification
Safety Analysis	10NOV2022	4.5.3.2, Appendix A. Ranges added for categorical (outlier) analysis of chemistry, hematology, and coagulation results.	Yes	Clarification
Safety Analysis	10NOV2022	4.5.4.2 MMRM analysis, which is included as an exploratory efficacy analysis, was removed from this section.	Yes	Correction/ Clarification
Interim Analysis	10NOV2022	5 Section 5 renamed since there will no longer be a planned interim analysis of efficacy.	Yes	Align with CSP amendment
General	25OCT2023	The SAP was updated to reflect changes introduced in the protocol amendment (v3.0).	Yes	Align with CSP amendment
Efficacy Analysis	17MAY2024	3.2, 4.1.2.1 Update to definition of the per protocol set. Difference from CSP noted in Section 2	No	Response to quality incident
General	17MAY2024	3.3.1.1, 3.3.2, 4.5 Details for distinguishing random glucose vs fasting glucose in the analysis	Yes	Response to dry run findings
General	17MAY2024	3.3.1.2 Analysis phase for listings of adverse events was defined.	Yes	Response to dry run findings

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
General	17MAY2024	3.3.2 A Week 52 analysis visit was specified for certain endpoints	Yes	Response to dry run findings
General	17MAY2024	4.1.2.2 Participants excluded from each analysis set will be listed with reason for exclusion	Yes	Clarification
General	17MAY2024	4.1.3.2 Only IPDs will be summarized and listed	Yes	Clarification
Efficacy Analysis	17MAY2024	4.2.3.1 Odds ratios will not be presented and unstratified estimator of difference in proportions will be used	Yes	Response to dry run findings
Efficacy Analysis	17MAY2024	4.2.3.2 Values of FAST used for analysis will be based on post-CDL calculations of FAST from values in the database.	Yes	Response to dry run findings
Efficacy Analysis	17MAY2024	4.2.3.3, 4.2.3.4 If models fail to converge or a collinearity issue is detected, models may be simplified.	Yes	Response to dry run findings
Efficacy Analysis	17MAY2024	4.2.3.4 Variables to be log-transformed prior to analysis were specified.	Yes	Response to dry run findings
Efficacy Analysis	17MAY2024	4.3 All measured concentration data for cotadutide participants will be summarized. Imputation for values <LLOQ specified.	Yes	Response to dry run findings
Efficacy Analysis	17MAY2024	4.4 Definitions for ADA analyses were rephrased and reordered, but not fundamentally changed.	Yes	Align with standard tables
Safety Analysis	17MAY2024	4.5 All abnormal random glucose values will be considered as ‘treatment emergent’ in analysis since there is no planned random glucose value prior to randomization.	Yes	Response to dry run finding

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D5671C00006 Part A data supporting the clinical study report (CSR). The reader is referred to the clinical study protocol (CSP) and the case report form (CRF) for details of study conduct and data collection.

This study was originally designed as a 2-part, Phase IIb/III, global, randomized, parallel-group, double-blind, placebo-controlled, multicenter study to assess the safety and efficacy of 300 and 600 µg cotadutide compared with placebo, given once daily as a subcutaneous injection administered via a multidose pen, in adults with non-cirrhotic non-alcoholic steatohepatitis (NASH) with fibrosis stage F2 or F3. After carefully considering several factors, foremost being the identification of other, more convenient treatments for patients with NASH, the sponsor made a strategic decision to discontinue development of cotadutide and recruitment into this study. Randomized participants and participants in active screening were allowed to continue participation. Given the reduced sample size, the primary goal of this study is to evaluate the safety and tolerability of cotadutide in participants with non-cirrhotic NASH with fibrosis. The originally planned Phase III portion of the study (Part B) will not be conducted and most references to it have been removed from this document.

Part A (Phase II) will assess the safety and efficacy of 300 µg and 600 µg cotadutide treatment.

In Part A, 300 participants were originally planned to be randomized to provide > 90% power for the test of each dose versus pooled placebo to detect a difference of 20% in NASH resolution assuming a placebo response rate of 15%. As a result of the decision to terminate recruitment, approximately 55 participants are planned to be randomized in the study.

At randomization, participants in Part A will be stratified by the presence/absence of type 2 diabetes mellitus (T2DM) and by fibrosis stage.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

In response to a quality incident (QE-341716), the per protocol set was updated to exclude participants from Site PPD due to GCP concerns. No other changes were made in the conduct of the study or in the planned analyses reported in this statistical analysis plan (SAP) with respect to the last CSP version.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

After all participants in Part A of the study have completed the study and clinical data lock for Part A has occurred, Part A will be unblinded and analyzed.

3.2 Analysis Populations

The following analysis populations are defined in Table 1:

Table 1 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Randomized	All participants randomized into the study.
FAS	All participants who have been randomized to and received at least 1 dose of IP.
PP	Subset of FAS population with evaluable post-baseline biopsy after at least 36 weeks of treatment. In response to a quality incident (QE-341716), participants from Site PPD will be excluded due to GCP concerns.
Safety	The Safety analysis set consists of all participants who have received at least 1 dose of IP. Erroneously treated participants (eg, those randomized to treatment A but actually given treatment B) are accounted for in the treatment group with the majority of estimated usage. In all cases, the dose level for analysis will correspond to the randomized dose.
PK	The PK population includes all participants who receive at least 1 dose of study intervention and have at least 1 complete intended PK sample containing detectable cotadutide concentrations.

FAS, full analysis set; ICF, informed consent form; IP, investigational product; PK, pharmacokinetic(s); PP, per protocol.

3.3 General Considerations

The primary analyses will be of safety. No formal hypothesis testing will be performed. Treatments will be compared in tables using descriptive statistics.

Exploratory efficacy analyses will use nominal 2-sided 5% significance levels (equivalent to nominal 1-sided 2.5% significance levels) unless otherwise stated.

The primary estimand of interest for the histological endpoints will use the treatment policy strategy. The treatment policy approach applies to intercurrent events of treatment discontinuation, deviations from the protocol titration schedule, changes in background medication, liver events, or use of prohibited medication or other protocol deviations.

For efficacy analyses, participants will be analyzed according to their randomized investigational product (IP) assignment and dose, irrespective of the treatment they actually received. Analyses will be performed using the full analysis set (FAS) and/or per protocol (PP) analysis sets, as appropriate. The FAS will include all randomized and treated participants who received at least 1 dose of IP irrespective of their protocol adherence, addition, or modification of background medications, discontinuation of study intervention or switches to alternative medications, and continued participation in the study.

All statistical summaries and analyses will be performed using Statistical Analysis System (SAS®) software version 9.4 or above (SAS Institute, Cary, North Carolina, USA).

3.3.1 General Study Level Definitions

3.3.1.1 Definition of Baseline

Baseline biopsy specimen refers to either historical biopsies or on-study biopsies obtained during the screening period. Central pathology review of the eligibility read will occur upon baseline biopsy specimen receipt and processing at the histopathology vendor. Central pathology review results will support patient eligibility and enrollment. This is referred to as the eligibility read and will serve as the baseline for histology analyses.

For continuous endpoints, the baseline value for statistical analysis is the last non-missing value on or prior to date and time (if available) of administration of the first dose of IP. If multiple measurements occur on the same day, the last non-missing value on or prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered as the baseline value. For electrocardiogram (ECG) parameters, the mean of the last set of triplicate measures prior to treatment is baseline.

For categorical endpoints, the last available record on or prior to the date of the first dose of study drug will be selected. If there are ties in terms of proximity to first dose, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings and '+' will be selected over '++' for urinalysis findings).

3.3.1.2 Definition of On-study and On-treatment

All adverse events (AEs) with start date on or after the date of first treatment will be considered on-study. On-treatment AEs are those occurring within the on-study period and within + 7 days of treatment discontinuation. All AEs leading to discontinuation of IP will be considered on-treatment.

On-study assessments (eg, vital signs, clinical laboratory tests, ECG) are defined as those occurring after the date and time (if available) of administration of the first dose of IP. On-

treatment assessments are defined as those occurring within the on-study period and on or before the date of administration of the last dose of IP with the following windows following treatment discontinuation:

- Fasting plasma glucose (FPG): +1 day from treatment discontinuation.
- Biopsy, liver tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL], and alkaline phosphatase [ALP]), and disease-specific biomarkers: + 30 days from treatment discontinuation.
- All other efficacy and safety: +7 days from treatment discontinuation.

Assessments other than AEs recorded on the day of first treatment and with time unavailable for the assessment or for the first dose, will be considered to be not in the on-study/on-treatment periods. For listings of AEs, analysis phase will be indicated as on-treatment if the AE starts within the on-treatment period, as 'pre-treatment' if it starts prior to the on-treatment period, and as 'post-treatment' if it starts after the on-treatment period.

3.3.1.3 Analysis Strata

Randomization stratification variables (T2DM status and fibrosis stage) are used in analyses either as analysis strata or as covariates. Stratum according to Interactive Response Technology/Randomization and Trial Supply Management (IRT/RTSM) will not be used for primary analysis. Rather, analysis strata for primary analysis will be based on the electronic CRF (eCRF) value for T2DM status and the fibrosis stage in the eligibility read.

3.3.1.4 Handling of Missing Dates

AE start and end date and concomitant medications (CMs) end date are imputed according to the rules described below. Start and end dates of treatment will not be imputed.

3.3.1.4.1 Imputation of AE End Date

Completely missing AE end dates are not imputed. Partial missing AE end dates are imputed as below:

- If the AE is ongoing, the end date is set to missing.
- If the AE is not ongoing, and if only the day is missing: Assume the last day of the collected month.
- If the AE is not ongoing, and both, the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed AE end date is after the end of study date, the AE is set to ongoing and the AE end date to missing.

3.3.1.4.2 Imputation of AE Start Date

Before proceeding with the AE start date imputation, the AE end date is imputed if missing, as described in the previous section.

For completely missing start dates, impute as first dose date unless the end date is prior to the first dose date, in which case impute as 01-JAN-YYYY of the same year as the AE end date.

Partial dates are imputed as described below:

If the day is missing and the month and year are different from the month and year of the first dose of IP, assume 01-MMM-YYYY. If the month and year are the same as the first dose of IP month and year and the end date is on or after (including ongoing/missing) the first dose of IP, then assume the date of the first dose of IP. If the month and year are the same as the first dose of IP month and year and the end date is prior to the first dose of IP, then assume the end date.

If the month is missing and the year is different from the year of first dose of IP, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of IP year and the end date is on or after (including ongoing/missing) the first dose of IP, then assume the date of the first dose of IP. If the year is the same as the first dose of IP and the end date is prior to the first dose of IP, then assume the end date.

After applying these rules, if the imputed AE start date is after a complete AE end date, then assume the same date as the complete AE end date; if the end date is missing and the imputed AE start date is after the end of study date, then assume the same date as the study end date.

3.3.1.4.3 Imputation of Concomitant Medication End Date

Completely missing CM end dates (where the CM is not ongoing) are imputed as the date of last dose, unless contradicted by the CM start date, in which case the end date will be the same as the CM start date. Partial missing CM end dates are imputed as below:

- If the CM is ongoing, the end date is set to missing.
- If the CM is not ongoing, and if only the day is missing: Assume the last day of the of the collected month.
- If the CM is not ongoing and both the day and the month are missing: Assume 31-DEC of the collected year.

After applying these rules, if the imputed CM is after the end of study date, the CM is set to ongoing and the CM end date to missing.

3.3.1.4.4 Imputation of Concomitant Medication Start Date

Missing CM start dates are not imputed.

3.3.1.4.5 Imputation of Treatment End Date

If date of end of treatment is unknown, it will be imputed as the date of last contact with the patient.

3.3.2 Visit Window

For the purpose of the statistical analysis, study findings are allocated to the analysis visit using analysis visit windows as described in Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8. Note, study day 1 refers to the date the participant received the first dose of IP.

Table 2 Analysis Visit Windows, Biopsy

Analysis Visit	Target Day	Day Range
Week 48	337	1 through end of study

Table 3 Analysis Visit Definitions, 12-lead dECG, Vital Signs, Abbreviated Physical Examination

Analysis Visit	Target Day	Day Range
Week 4	29	2-42
Week 8	57	43-70
Week 12	85	71-98
Week 16	113	99-126
Week 20	141	127-154
Week 24	169	155-196
Week 32	225	197-252
Week 40	281	253-308
Week 48	337	309-351
Week 52	365	352-385

dECG, digital electrocardiogram.

Table 4 Analysis Visit Definitions, Clinical Laboratory Assessments Including eGFR and MELD but Excluding Fasting Glucose (Safety)

Analysis Visit	Target Day	Day Range
Week 4	29	2-42
Week 8	57	43-70
Week 12	85	71-98
Week 16	113	99-126
Week 20	141	127-154
Week 24	169	155-196
Week 32	225	197-280

Table 4 Analysis Visit Definitions, Clinical Laboratory Assessments Including eGFR and MELD but Excluding Fasting Glucose (Safety)

Analysis Visit	Target Day	Day Range
Week 48	337	281-351
Week 52	365	352-385

Due to fasting at the Week 48 visit, random glucose will not be presented for the Week 48 analysis visit.
eGFR, estimated glomerular filtration rate; MELD, model for end-stage liver disease.

Table 5 Analysis Visit Definitions, Amylase, Lipase, Coagulation

Analysis Visit	Target Day	Day Range
Week 24	169	2-196
Week 32	225	197-280
Week 48	337	281-378

Table 6 Analysis Visit Definitions, Calcitonin, FibroScan, FAST, Agile 3+, BARD, Fasting Serum Lipid Panel, ELF, Pro-C3, FIB-4, Fasting Plasma Glucose (Efficacy), Fasting Glucose (Safety), C-peptide, Adiponectin

Analysis Visit	Target Day	Day Range
Week 48	337	2-378

BARD, BMI, AST/ALT ratio, diabetes; ELF, enhanced liver fibrosis; FAST, FibroScan-ALT; FIB-4, fibrosis-4; Pro-C3, released N-terminal propeptide of type III collagen.

Table 7 Analysis Visit Definitions, PK, and ADA

Analysis Visit	Target Day	Day Range
Week 4	29	2-57
Week 12	85	58-127
Week 24	169	128-253
Week 48	337	254-378

ADA, anti-drug antibody; PK, pharmacokinetic(s).

Table 8 Analysis Visit Definitions, HbA1c, Urine Albumin, Creatinine

Analysis Visit	Target Day	Day Range
Week 12	85	2-127
Week 24	169	128-253
Week 48	337	254-378

HbA1c, hemoglobin A1c.

Multiple biopsy samples within an analysis visit window are not expected. Although unlikely, if multiple histology samples are collected in the Week 48 analysis visit window, then the

histology sample collected closest to the target date will be selected (using the later sample as a tiebreaker).

If multiple, valid, non-missing, continuous measurements exist in an analysis visit window, records will be chosen based on the following rules:

1 The record closest to the target day for that visit will be selected.
2 If there are 2 records that are equidistant from the target day based on date, the later record will be selected.
3 In general, if there is more than 1 record on the selected day, the average will be taken.
4 For serum creatinine, if both enzymatic and regular creatinine are measured in the course of the study, both types of tests will be analyzed as a single parameter. If both enzymatic and regular creatinine are collected from the same blood sample and are analyzable, regular creatinine will be selected for analysis.

If multiple, valid, non-missing, categorical measurements exist in an analysis visit window, records will be chosen based on the following rules:

1 The record closest to the target day for that visit will be selected.
2 If there are 2 records that are equidistant from the target day based on date, the later record will be selected.
3 In general, if there is more than 1 record on the selected day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings and '++' will be selected over '+' for urinalysis findings).

If a laboratory test was performed within the analysis visit window, the result collected under a fasting condition will be used.

3.3.3 Handling of Unscheduled Visits

If there is more than 1 assessment in the same time window, 1 assessment will be chosen for inclusion in analysis based on rules described in Section 3.3.2. All scheduled and unscheduled assessments will be presented in the listings.

3.3.4 Multiplicity/Multiple Comparisons

No formal hypothesis testing will be performed, and all p-values are nominal. Therefore, no adjustments for multiplicity will be made.

3.3.5 Handling of Protocol Deviations in Study Analysis

The list of important protocol deviations (IPDs) is provided in the Protocol Deviation Plan.

4 STATISTICAL ANALYSIS

The safety population will be used as the primary population for safety analyses. Efficacy analyses will be performed using the FAS and/or PP analysis sets, as appropriate.

4.1 Study Population

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

None

4.1.1.2 Presentation

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

- # enrolled
- # randomized
- # receiving at least 1 dose
- # completed treatment/discontinued treatment
- # completed study/withdrew from study
- # not discontinued/discontinued from treatment at Week 48

Randomization code and assigned kit ID will also be listed.

A listing including all standardized disposition terms will be also provided for all discontinued participants. Both the table and the listing will be based on the all enrolled participants population.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis sets are defined in Section 3.2.

Possible reasons for exclusion from analysis sets will be:

- Randomized set: Participant not randomized.
- FAS: Participant not randomized OR participant did not receive at least 1 dose of the IP.
- PP: Participant not randomized OR participant did not receive at least 1 dose of the IP OR did not have evaluable post-baseline biopsy after at least 36 weeks of treatment OR participant excluded due to site GCP concerns (Site PPD
- Safety set: Participant did not receive at least 1 dose of the IP.

- PK (pharmacokinetics) set: Participant did not receive at least 1 dose of the IP OR participant did not have at least 1 detectable cotadutide concentration.

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 in each part. The table will be based on the all enrolled participants population. Listings of all randomized participants excluded from the FAS, PP, safety, or PK population will be also provided including reason for exclusion from the population.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

The protocol deviations will be captured during the study. IPDs are described in Section 3.3.5.

4.1.3.2 Presentation

The number and percentage of participants with at least 1 IPD will be summarized for each treatment group and overall in each part in the FAS population. All IPDs will be also listed for all participants included in the FAS population.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic variables include age, age category (< 50 years; ≥ 50 to < 65 years; ≥ 65 years), sex, race, ethnic group, region, and country. Age at screening and year of birth is collected directly on the CRF; month and day of birth will not be entered. The age at screening used for analysis will be the directly entered value. For determination of age post-screening, refer to Section 4.2.3.2.

Regions will be defined as:

- US: United States
- Asia: Japan, South Korea, Malaysia, Thailand, and Taiwan
- Rest of World: (all other countries)

4.1.4.2 Presentation

Demographic variables will be summarized for each treatment group and overall in the FAS population. They will be also listed for all participants included in the FAS population.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include height (cm), weight (kg), body mass index (BMI) (kg/m^2), and BMI category. BMI (kg/m^2) is calculated as weight (kg) divided by the square of height (cm)/100.

4.1.5.2 Presentation

Baseline variables will be summarized for each treatment group and overall in the FAS population. Continuous variables will be summarized using n, mean, median, standard deviation (SD), minimum, and maximum; categorical variables will be summarized using number and percent of participants.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

sease characteristics and comorbidities include baseline liver fibrosis stage (F2 and F3) and T2DM status, Non-alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) (overall score and steatosis, lobular inflammation, and ballooning components), FibroScan (liver stiffness measurement [LSM] and controlled attenuation parameter [CAP]), enhanced liver fibrosis (ELF) score, CMs of vitamin E and pioglitazone, lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides), ALT, AST, gamma glutamyl transferase (GGT), liver biomarkers (Pro-C3, FIB-4, APRI, NFS, BARD score, FibroScan-AST [FAST] score, and Agile 3+). Hemoglobin A1c (HbA1c) will be analyzed as a continuous variable as well as categorically (< 5.7%, 5.7% to 6.4%, ≥ 6.5%). Model for End-Stage Liver Disease (MELD) score, fasting plasma glucose, (total and high molecular weight) adiponectin, C-peptide, and systolic blood pressure (SBP) at baseline will be included. Use of lipid-lowering therapies or T2DM therapies will be included.

If both direct and calculated LDL lab codes are entered, they will be combined into a single parameter for analysis and used interchangeably.

Details of screening biopsy (as an on-study procedure or from a historical sample) will be summarized by treatment group, including timing relative to randomization.

4.1.6.2 Presentation

Baseline disease characteristic variables will be summarized for each treatment group and overall in the FAS population. Continuous variables will be summarized using n, mean, median, SD, minimum, and maximum; categorical variables will be summarized using number and percent of participants.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Complete medical history will include history and current medical conditions past or present, including cardiovascular (CV) disorders; respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatological, psychiatric, genitourinary, or any other diseases or disorders; drug and surgical history; and history of alcohol and tobacco use. Disease-related and relevant medical history are coded in Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or higher.

4.1.7.2 Presentation

Relevant and disease-related medical history will be presented in summary tables as number and percentage of participants by System Organ Class (SOC) and Preferred Term (PT) for each treatment group and overall. Participants with multiple events in the same SOC/PT will be counted only once in that SOC/PT. Participants with events in more than 1 SOC/PT will be counted once in each of those SOC/PT. Tables will be sorted by international order for SOC and in alphabetical order for PT. The tables will be based on the safety population.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

The World Health Organization (WHO) Drug Dictionary March 2022 B3 Global or higher is used to classify medications by WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study will be recorded along with reason for use, dates of administration including start and end dates, and dosage information including dose and frequency.

Restricted and prohibited medications are described in the CSP. Potential prohibited and restricted CMs are identified by ATC code lists or flagged by the study physician.

For the purpose of analysis, prohibited medications will be determined as follows:

- Therapies associated with development of NAFLD such as methotrexate, tamoxifen, amiodarone, or long-term use of tetracyclines or systemic corticosteroids with start date < 90 days prior to date of biopsy used for screening. “Long-term use” is defined as a duration greater than 14 days.
- Therapies in classes under investigation for the treatment of NASH (except for SGLT-2 inhibitors), such as obeticholic acid, pioglitazone, and vitamin E with start date < 180 days prior to date of biopsy used for screening. In the case of pioglitazone or high-dose vitamin E, these drugs are restricted during the study unless the participant has been on a stable dose for at least 180 days prior to baseline biopsy (historical or on-study).

- Glucagon-like peptide-1 (GLP-1) receptor agonists and GLP-1 receptor agonist containing therapies with start date < 90 days prior to date of biopsy used for screening.
- Weight loss drugs with start date < 90 days prior to date of biopsy used for screening.
- Herbal preparations or dietary supplements marketed for control of body weight or appetite or with any suspected hepatotoxicity with start date < 14 days prior to first screening visit.
- In general, timing criteria will be assumed to be met for categorization as a prohibited medication when ambiguous due to missing information for start/end dates.

The imputation method described in Section 3.3.1 is used in case of medication stop date partially missing. Completely missing stop dates will not be imputed. Both completely missing and partially missing CM start dates are not imputed.

After the end date imputation, the medications will be classified as either prior or concomitant (but not both) according to its stop date. Prior medication is defined as any medication with a stop date prior to the first dose of study drug (exclusive). CM is defined as any medication with a stop date on or after the first dose of study drug, or any medication that is ongoing at study end. Medications with completely missing stop date are classified as concomitant.

4.1.8.2 Presentation

The number and percentage of participants with at least 1 CM (excluding prohibited medications) and the number and percentage of participants by ATC level 4 (therapeutic subgroup) and product name will be provided using the Safety population.

The number and percentage of participants with at least 1 prohibited CM and the number and percentage of participants by ATC level 4 (therapeutic subgroup) and product name will be provided using the Safety population by period.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

When participants are dosed at the site, they will self-administer the study intervention under medical supervision from the investigator or designee. The date and time of dose administered in the clinic will be recorded in the source documents and in the eCRF.

While the number of returned pens is counted, pens will not otherwise be inspected for compliance.

4.1.9.2 Presentation

Given the limitations in data collection, study drug compliance will not be summarized.

4.2 Endpoint Analyses

The primary analyses will be of safety. No formal hypothesis testing will be performed. Treatments will be compared in tables using descriptive statistics. All efficacy analyses are exploratory.

4.2.1 Primary Endpoint

The primary objective is to evaluate the safety and tolerability of cotadutide as compared with placebo in participants with non-cirrhotic NASH with fibrosis.

Primary safety endpoints:

Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical and laboratory assessments, and ECGs.

Assessments related to AEs cover:

- Occurrence/frequency
- Relationship to IP as assessed by the investigator
- Intensity
- Seriousness
- Death
- AEs leading to discontinuation of IP
- AEs leading to dose reduction of IP
- AEs of special interest
- Adjudicated CV events including major adverse cardiovascular event (MACE), selected liver events, diabetic ketoacidosis, pancreatitis, pancreatic carcinoma, and thyroid carcinoma

Vital signs parameters include SBP, diastolic blood pressure (DBP), and pulse.

Assessments cover:

- Observed value
- Absolute change from baseline values over time
- Abnormality at least once on treatment

Laboratory parameters include clinical chemistry (including MELD score) and hematology parameters as well as urinalysis.

Assessments cover:

- Observed value
- Absolute change from baseline values over time
- Abnormality/clinically significant abnormality in laboratory parameters at least once on treatment
- Treatment-emergent increase in hematuria, proteinuria, and glucose in urinalysis defined as change from negative/trace at baseline to ++, +++, or ++++ at any visit after baseline or an increase of at least ++

Electrocardiogram measurements include heart rate, RR, PR, QRS, and QT intervals. Derived variables cover QTcF.

Assessments cover:

- Observed value
- Absolute change from baseline values over time
- ECG parameters fulfilling potentially clinically significant criteria at any time during treatment, including QRS duration > 118 ms, PR interval > 210 ms, RR < 600 ms (resting heart rate > 100 bpm), and RR > 1330 ms (resting heart rate < 45 bpm)
- QTcF exceeding 450, 480, and 500 ms at any time during treatment
- Change in QTcF at any time during treatment as compared to baseline exceeding 30 ms and 60 ms

For details of the safety analysis, refer to Section 4.5.

A second primary objective is ‘to assess the immunogenicity of cotadutide’ with associated endpoint “incidence of ADAs to cotadutide and titer during treatment and follow-up.” Details of analysis of anti-drug antibodies (ADAs) can be found in Section 4.4.

4.2.2 Secondary Endpoints

There are no secondary endpoints.

4.2.3 Other Endpoints

4.2.3.1 Definition

Tertiary/exploratory endpoints will be tested versus placebo at the 2-sided nominal alpha 5% level, without consideration of multiplicity:

The following are histological endpoints, to be assessed centrally 1) by independent pathologists and 2) by artificial intelligence, as detailed in the Central Histopathology Review

Charter. Analysis of continuous histological scores, if included, will be based solely on values provided by artificial intelligence.

- Proportion of participants with resolution of NASH without worsening of liver fibrosis based on biopsy at Week 48
- Proportion of participants with improvement of liver fibrosis by at least 1 stage without worsening of NASH based on biopsy at Week 48. (Worsening of NASH is defined as any increase in the ballooning, inflammation, or steatosis scores even if total NAS does not increase.)
- Proportion of participants with both resolution of NASH and improvement in fibrosis by at least 1 stage based on biopsy at Week 48
- Proportion of participants with improvement in fibrosis by at least 1 stage based on biopsy at Week 48
- Proportion of participants with improvement in NAS based on biopsy at Week 48
- Change from baseline in NAS based on biopsy at Week 48
- Change from baseline in fibrosis stage based on biopsy at Week 48
- Proportion of participants with progression, no change, or regression in fibrosis stage based on biopsy at Week 48
- Proportion of participants with improvement in key histological features of NASH on biopsy at Week 48, including:
  - Inflammation
  - Steatosis
  - Ballooning

Below are other exploratory/tertiary endpoints not based on biopsy:

- Change from baseline in liver enzymes including ALT and AST through Week 48
- Change from baseline in triglycerides, LDL cholesterol, and HDL cholesterol, non-HDL cholesterol, and total cholesterol, and HbA1c through Week 48
- Cotadutide PK exposure will be summarized and compared with prior data for consistency
- Change from baseline at Week 48 in:
  - LSM as assessed by FibroScan
  - Percentage CAP as assessed by FibroScan
- Changes from baseline at Week 48 in non-invasive disease-specific biomarkers, including but not limited to:
  - Pro-C3

  - ELF score
  - FIB-4
  - APRI
  - NFS
  - BARD score
  - FAST score
  - Agile 3+
- Percent change from baseline in body weight at Week 48
- Change from baseline in FPG, adiponectin, and C-peptide at Week 48
  - Both total and high molecular weight adiponectin will be assessed
- Change from baseline in SBP through Week 48

4.2.3.2 Derivations

Binary endpoints of resolution of NASH and fibrosis improvement will be derived from datasets transferred from the histopathology vendor. These datasets will include NAS components, NAS and fibrosis stages, but not derived endpoints (such as NASH resolution). Final scores for each NAS component and fibrosis stage based on the process described in Central Histopathology Review Charter will be used to derive variables for analysis. Because resolution of NASH allows steatosis score of any degree (from 0 to 3), if the steatosis score is not evaluable, resolution of NASH will still be concluded if there is a ballooning score of 0 and an inflammation score of 0 to 1.

Analysis of absolute change from baseline will use the post-baseline value minus the baseline value.

Analysis of percent change form baseline will use the natural log-transformed post-baseline value minus the natural log-transformed baseline value (log ratio). Calculation of summary measures with least squares mean (LSMEAN) or least squares mean difference (LSMD) values from analysis of covariance (ANCOVA) or mixed model for repeated measures (MMRM) using log-transformed values is described in Table 9.

Table 9 Formula for ANCOVA or MMRM Using Log-transformed Values

Quantity	Computation Method
Estimate for Percent Change from Baseline	100 × [exp(LSMEAN change from baseline in natural logarithm) – 1]
LCL for Percent Change from Baseline	100 × [exp(LCL for LSMEAN change from baseline in natural logarithm) – 1]

Table 9 Formula for ANCOVA or MMRM Using Log-transformed Values

Quantity	Computation Method
UCL for Percent Change from Baseline	100 × [exp(UCL for LSMEAN change from baseline in natural logarithm) – 1]
Estimate for Ratio Change from Baseline, Cotadutide relative to Control	exp(LSMD in mean change from baseline in natural logarithm)
LCL for Ratio Change from Baseline, Cotadutide relative to Control	exp(LCL for LSMD in change from baseline in natural logarithm)
UCL for Ratio Change from Baseline, Cotadutide relative to Control	exp(UCL for LSMD in change from baseline in natural logarithm)

ANCOVA, analysis of covariance; LCL, lower confidence limit; LSMEAN, least square mean; MMRM, mixed model for repeated measures; exp, exponent; UCL, upper confidence limit.

If both direct and calculated LDL lab codes are entered, they will be combined into a single parameter for analysis.

Age post-screening is required for some endpoint derivations and will be based on the latest date of collection for values of components used to determine the score. Age at screening and year of birth is collected directly on the CRF; month and day of birth will not be entered. The age at screening used for analysis will be the directly entered value. For determination of age post-screening, a complete birth date needs to be imputed and the following algorithm will be used:

- If (age at screening) = (year of screening) – (year of birth), then impute the month and day of birth date as the month and day of the screen date. If screening falls on 29 February, then impute as 28 February instead.

If (age at screening) = (year of screening) – (year of birth) – 1, then impute the month and day of birth date as the month and day of the day after the screen date. If that date falls on 29 February, then impute as 1 March instead.

Agile-3+ will be calculated as described in (Sanyal et al 2023):

- $Agile\ 3+= \frac{e^{Xb}}{1+e^{Xb}}$
- Where Xb = -3.92368+2.29714 × ln(LSM) – 0.00902 × platelets – 0.98633 × (AST/ALT ratio)$^{-1}$ +1.08636 × Diabetes status – 0.38581 × Sex + 0.03018 × Age
- Variables: LSM in units of kPa, platelets in units of 10^9/L, AST/ALT ratio based on AST and ALT in any consistent units, age in units of years, diabetes status: yes = 1, no = 0 and sex: male = 1, female = 0

Values of FAST used for analysis will be calculated based on values of LSM, CAP, and AST in the database (LSM and CAP from FIBSCAN module and AST from central laboratory) as described in (Newsome et al 2020):

- $FAST = \frac{e^{Xb}}{1+e^{Xb}}$
- Where $Xb = -1.65 + 1.07 \times \ln(LSM) + 2.66 \times 10^{-8} \times CAP^3 - 63.3 \times AST^{-1}$
- Variables: LSM in units of kPa, CAP in units of dB/m, and AST in units of IU/L

BARD will be calculated as described in (Harrison et al 2008), as a score between 0 and 4 where:

- 1 point is assigned for BMI ≥ 28 kg/m^2
- 2 points are assigned for an AST/ALT ratio ≥ 0.8
- 1 point is assigned for T2DM

4.2.3.3 Handling of Dropouts and Missing Data

A post-baseline liver biopsy is planned for each participant at Week 48. Participants who discontinue study intervention early will have an early discontinuation visit. Participants will be encouraged to have the biopsy at Week 48 as planned in the CSP schedule of activities. Participants who are unwilling or unable to wait until Week 48 will have the biopsy procedure as part of the early discontinuation visit if they have received study intervention for at least 36 weeks. Participants who have not been on study intervention for at least 36 weeks will not have a biopsy at the early discontinuation visit.

Unless stated otherwise, the following rules will be used for missing data in exploratory endpoints:

- For biopsy endpoints analysis using the FAS analysis set, will impute missing observations as non-responders while analysis using the PP analysis set will exclude participants with missing data.
- Missing observations for ordinal endpoints will not be imputed, unless otherwise stated.
- Missing observations for continuous endpoints for analyses including multiple post-baseline timepoints will not be imputed.
- Missing observations for continuous endpoints for analyses including only a single post-baseline timepoint will be imputed using multiple imputation (monotone regression) separately by randomized treatment arm with stratification variables (baseline fibrosis stage and T2DM status) and baseline measurement for the endpoint as independent variables. If an issue is encountered for fitting an imputation model (eg, collinearity with intercept), a simplified imputation model may be used.

4.2.3.4 Primary Analysis of Other Endpoints

Unless otherwise indicated, analyses of tertiary/exploratory histological endpoints and continuous exploratory endpoints at Week 48 will include both on- and off-treatment measurements while analyses of endpoints at multiple timepoints through Week 48 will only include on-treatment measurements. The treatment effect for binary exploratory endpoints will be analyzed by the Cochran-Mantel-Haenszel (CMH) test, stratified for T2DM presence and F2/F3 fibrosis stages. The difference in proportion (unstratified response difference) with Miettinen-Nurminen (ie, score-based; without stratification) 95% confidence interval, and nominal p-value from CMH chi-square test will be provided.

Continuous endpoints summarized for a single post-baseline timepoint (Week 48) will be analyzed using ANCOVA with baseline, baseline T2DM status, baseline fibrosis stage, and treatment as independent variables, using multiple imputation. If an issue is encountered for fitting an ANCOVA model (eg, collinearity with intercept), a simplified model may be used. For analysis of (absolute) change from baseline, endpoints will be analyzed without transformation and LSMEAN change from baseline by treatment; the treatment effect as the LSMD will be reported as point estimates and 95% confidence intervals with p-values provided for treatment effect. For analysis of percent change from baseline, ANCOVA will be performed using log-transformed values. Point estimates and 95% confidence intervals of percent change from baseline by treatment and ratio change from baseline will be reported with a nominal p-value for treatment effect (Section 4.2.3.2). Rubin's rules (Rubin 1987) will be used to pool LSMEAN and LSMD values and associated standard errors across multiply imputed datasets and will provide the reported estimates and p-values. The following variables will be log-transformed: ALT, AST, APRI, triglycerides, PRO-C3, FIB-4, FPG, (total and high molecular weight) adiponectin, and C-peptide. Other variables may be log-transformed if required.

Change from baseline in continuous fibrosis scores from artificial intelligence, if available, will be analyzed by ANCOVA, as described above. Additionally, continuous scores from artificial intelligence for key histological features of NASH (inflammation, steatosis, ballooning), if available, may be analyzed using ANCOVA. Change from baseline in fibrosis stage (non-continuous scores) based on biopsy at Week 48 will not be analyzed by ANCOVA, but will instead be summarized descriptively by treatment using shift tables.

Analysis of continuous endpoints at multiple timepoints will be performed using MMRM adjusting for baseline value, fibrosis stage (F2/F3), T2DM status, analysis visit, treatment, the interaction of treatment and analysis visit and the interaction of baseline value and analysis visit. Only on-treatment data (Section 3.3.1) will be included in the model and missing data will not be imputed. An unstructured covariance structure will be used. If the computational algorithm fails to converge, the following structures will be tested in the following order:

Toeplitz, first-order autoregressive (AR[1]), and compound symmetry. Alternatively, covariates may be dropped from the model. Estimates, standard errors, and 95% confidence intervals of mean change from baseline or percent change from baseline will be reported by treatment and analysis visit. Restricted Maximum Likelihood estimation will be used in MMRM analyses.

4.2.3.5 Additional Analyses of Other Endpoints

None

4.2.3.6 Subgroup Analyses

Analysis of the following tertiary/exploratory endpoints will be repeated for subgroups:

- Proportion of participants with resolution of NASH without worsening of liver fibrosis based on biopsy at Week 48
- Proportion of participants with improvement of liver fibrosis by at least 1 stage without worsening of NASH based on biopsy at Week 48

For each subgroup, 95% confidence intervals of the difference in proportions (response difference) will be computed using the method of Miettinen-Nurminen (ie, score-based; without stratification) as well as p-values for general association (chi-square test). Results will be presented as Forest plots as well as corresponding tables.

Subgroups:

- Participants with and without T2DM at randomization (as-randomized strata)
- Fibrosis category (F2/F3) at randomization (as-randomized strata)

4.3 Pharmacokinetic Endpoint(s)

4.3.1 Analysis

PK results from sparse sample collection will be descriptively summarized.

4.3.2 Definitions and Derivations

For computing summary statistics, concentrations under the lower limit of quantification (LLOQ) will be imputed as 0 if prior to the first dose or as LLOQ/2 otherwise. Such concentrations will be displayed as '< [LLOQ]' in listings.

4.3.3 Presentation

Plasma concentration will be presented by randomized arm and by visit in a summary table. The table will be based on the PK population.

4.4 Immunogenicity

Immunogenicity assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in the CSP (Section 1.3.2). The ADA result from each sample will be reported as either positive or negative. ADA titer will be reported for samples confirmed positive for the presence of ADAs. Presence of ADA cross-reactive to GLP-1 and glucagon may be reported for samples confirmed positive for the presence of ADAs.

The percentage of ADA-positive patients in each category defined below will be calculated, using the number of participants in the safety analysis set by treatment group as the denominator.

- ADA positive at baseline and/or post-baseline (ADA prevalence): ADA positive at any visit, including baseline.
- TE-ADA positive (ADA incidence): The composite of both treatment-induced and treatment-boosted ADA. There is ADA incidence if either treatment induced ADA or treatment-boosted ADA is observed.
- Treatment-induced ADA positive: ADA positive post-baseline and not detected at baseline.
- Treatment-boosted ADA positive: a baseline positive ADA titer that was boosted to a 4-fold or higher level (greater than the analytical variance of the assay) following drug administration.
- Non-TE-ADA positive: ADA positive but not fulfilling the definition of TE-ADA positive (ie, ADA positive baseline sample and at least 1 post-baseline sample ADA positive, but participant was not treatment-boosted ADA positive).
- Both baseline and post-baseline positive: ADA positive for at least 1 sample post-baseline and an ADA positive sample at baseline.
- Only baseline positive: ADA not detected for any sample post-baseline and there was an ADA positive sample at baseline.
- ADA persistently positive: defined as having at least 2 post-baseline ADA-positive measurements with at least 16 weeks (112 days) between the first and last positive measurement or at least 2 post-baseline ADA-positive measurements with an ADA-positive result at the last available assessment. The category includes participants meeting these criteria who are ADA positive at baseline.
- ADA transiently positive: defined as having at least 1 post-baseline ADA-positive measurement and not fulfilling the conditions for persistently positive. The category includes participants meeting these criteria who are ADA positive at baseline.

If ADA cross-reactivity to GLP-1 and/or glucagon is measured, the below will also be reported, using the number of participants in the safety analysis set by treatment group as the denominator.

- ADA cross-reactive to GLP-1 at baseline and/or post-baseline
- Treatment-induced ADA with cross-reactivity to GLP-1
- ADA cross-reactive to glucagon at baseline and/or post-baseline
- Treatment-induced ADA with cross-reactivity to glucagon

ADA positivity and associated titers will be reported by analysis visit. If measured, ADA with cross-reactivity to GLP-1 and/or ADA with cross-reactivity to glucagon will be summarized by visit with associated titers.

The impact of ADA on PK and association with treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs), including analysis of events with the SOC of "Immune system disorders" may be assessed, if data permits.

4.5 Safety Analyses

Safety analyses include exposure, AEs, clinical laboratory results, vital signs, and ECGs. Safety events and findings will be summarized by treatment group. Erroneously treated participants (eg, those randomized to treatment A but actually given treatment B) are accounted for in the treatment group with the majority estimated usage. The majority estimated usage will be determined based on which treatment had more kits dispensed (not including kits returned unused). In the case of a tie, the randomized treatment will be used for safety analyses. In all cases, the dose group will be the same as randomized dose level.

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

Laboratory, vital sign, and ECG interval abnormalities will be considered treatment emergent if collected after the first dose and if the result is numerically more extreme than baseline – ie, the result is lower than baseline for low abnormalities and higher than baseline for high abnormalities. In cases of a missing baseline value (and for all random glucose abnormalities, since there is no planned baseline), any post-baseline value meeting the post-baseline criteria will be considered to be an abnormality. 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 ++.

4.5.1 Exposure

4.5.1.1 Definitions and Derivations

As per the CSP, participants start the subcutaneous injections of the study IP at day 1. Study IP is dispensed to the participant for self-administration at home.

Exposure (days) is calculated only for participants in the safety population as the total number of days on study drug (ie, gaps in dosing due to study drug interruption will not be taken-out from the calculation). Exposure is calculated as the study drug dose last date minus study drug dose first date plus 1.

Cumulative exposure (days) is also computed based on exposure, using the following duration (days) categories:

- 12 weeks (≥ 84 days)
- 24 weeks (≥ 168 days)
- 48 weeks (≥ 336 days)

4.5.1.2 Presentation

Exposure duration and cumulative exposure will be presented in a summary table for each treatment group. Maximum titrated dose (n % at each dose) will be summarized for each treatment group. The tables will be based on the safety population.

Exposure will be listed for the safety population.

4.5.2 Adverse Events

4.5.2.1 Definitions and Derivations

AEs will be coded with MedDRA version 25.0 or later. Additional details on AE reporting are provided in the CSP.

AEs of special interest (AESIs) for this study include:

- Nausea
- Vomiting
- Increased Heart Rate
- Injection Site Reaction
- Blood Pressure Alteration (Hypotension/Hypertension)
- Hypoglycemia
- Diabetic ketoacidosis
- Anti-drug Antibody

- Pancreatitis
- Pancreatic carcinoma
- Thyroid Carcinoma
- Acute Renal Failure Secondary to Dehydration
- Drug-induced liver injury (DILI)
- Cardiovascular events
- Gallbladder-related disease

The duration of an AE is calculated as the end date of the AE – start date of the AE + 1. Duration is calculated for complete dates only. Imputed dates should not be used. If one of the dates is missing or partially missing, the duration is missing.

3-point and 5-point MACEs are defined as a composite of the below adjudicated events.

3- and 5-point MACE:

- Death by any cause
- Cerebrovascular events- Stroke (non-fatal)
- Cardiac ischemic events – Myocardial Infarction (non-fatal)

5-point MACE only:

- Cardiac ischemic events – Hospitalization for Unstable Angina
- Hospitalization for heart failure

4.5.2.2 Presentation

AEs will be summarized for each treatment group. The AE tables will be based on the safety analysis set. Summary tables will include all on-study AEs. Select AE and AESI summaries will be repeated for all on-treatment events as appropriate.

Summary tables are listed below.

An overview table will contain summaries of the number and percentage of participants with the following:

- Any AE
- Any AE considered related to IP
- Any AE leading to death
- Any SAE
- Any AE leading to discontinuation of IP

- Any AE leading to a reduction of IP dose
- Any AE leading to withdrawal from the study

The following summary tables will be presented by SOC and PT:

- Any AE
- Any AE considered related to IP
- Any AE leading to death
- Any SAE
- Any AE leading to discontinuation of IP
- Any AE leading to a reduction of IP dose
- Any AE leading to withdrawal from the study
- The number and percentage of participants with any AEs by maximum reported intensity

On-study AESIs will be summarized as number and percentage of participants with the following:

- Any AESI
- Each specific AESI will also be summarized, overall and by maximum intensity
- Each specific AESI will be summarized by SOC and PT
- Select AESI summaries will be repeated for all on-treatment events as appropriate

Adjudicated events (separate on-study and on-treatment analyses) will be summarized as number and percentage of participants with the following:

- Any liver event (hepatic decompensation, clinical cirrhosis, DILI, hepatocellular carcinoma, or death from any cause)
- Events of hepatic decompensation
  - Clinically apparent ascites requiring treatment
  - Complication of ascites (eg, spontaneous bacterial peritonitis, diuretic-resistant ascites [refractory ascites], hepato-pleural effusion)
  - Hepatic encephalopathy of Grade 2 or above (according to the West Haven criteria) requiring treatment
  - Portal hypertension-related upper gastrointestinal bleeding identified by endoscopy and requiring hospitalization, including events of bleeding from esophageal varices, gastric varices, and portal hypertensive gastropathy
- Clinical cirrhosis
- DILI
- Hepatocellular carcinoma

- Death by any cause
- 3-point MACE
- 5-point MACE
- CV death
- Cardiac ischemic events – Myocardial Infarction (non-fatal)
- Cardiac ischemic events – Myocardial Infarction (any)
- Cerebrovascular events- Stroke (non-fatal)
- Cerebrovascular events- Stroke (any)
- Cardiac ischemic events- Hospitalization for Unstable Angina
- Hospitalization for heart failure
- Diabetic ketoacidosis
- Thyroid carcinoma
- Pancreatitis
- Pancreatic carcinoma

Additional analyses will be provided for adjudicated events, if required.

Where number of participants with AEs are summarized by SOC and PT, participants with multiple events in the same SOC/PT are counted only once in that SOC/PT. Participants with events in more than 1 SOC/PT are counted once in each of those SOCs/PTs. Participants with multiple occurrences of the same AESI will be counted once at the maximum observed severity. Tables will be sorted by international order for SOC and in alphabetical order for PT.

Additionally, the following tables will be presented:

- The number and percentage of participants with non-serious AEs occurring with a frequency > 5.0% in any treatment group for each SOC and PT. This table will be produced as a separate pdf output to meet clinical trial transparency requirements and not for inclusion in the CSR.

A list of key participant information for participants with AEs with outcome of death, participants with SAEs, and participants with AEs leading to discontinuation of IP will be provided. The durations reported in these tables will be derived only for fully completed dates as below:

- Time from first dose of IP to AE (in days) will be calculated as the AE start date minus date of dose +1.

- Time from first dose to death (in days) will be calculated as the date of death minus date of dose +1.
- The same approach will be used for deriving time from start of treatment to AE becoming serious or discontinuation.
- Time from last dose prior to AE start and last dose prior to death will be calculated as the date of death minus the date of last dose prior to AE/death +1.

All AEs will be listed (including AEs before the date of first dose).

4.5.3 Clinical Laboratory Results

4.5.3.1 Definitions and Derivations

Clinical laboratory safety tests are performed in a central clinical laboratory.

Clinical laboratory safety tests are specified in Table 10, with clinical results to be reported in SI units as well as conventional units where indicated.

Table 10 Laboratory Safety Variables

Hematology/hemostasis (whole blood)	**Clinical chemistry (plasma or serum)**
B-Hemoglobin (SI: g/L and conventional: g/dL)	S/P-Creatinine (SI: umol/L and conventional: mg/dL)
B-Leukocyte count (10^9/L)	S/P-Total Bilirubin (TBL) (SI: umol/L and conventional: mg/dL)
B-Leukocyte differential count (absolute count) (10^9/L)	S/P-Alkaline phosphatase (SI: µkat/L and conventional: U/L)
B-Platelet count (10^9/L)	S/P-AST (SI: µkat/L and conventional: U/L)
B-Red blood cell count (10^{12}/L)	S/P-ALT (SI: µkat/L and conventional: U/L)
B-Hematocrit (ratio)	S/P-Albumin (SI: g/L and conventional: g/dL)
B-Mean corpuscular hemoglobin concentration (SI: g/L and conventional: g/dL)	S/P-Potassium (SI: mmol/L and conventional: mEq/L)
B-Mean corpuscular volume (µm^3)	S/P-Calcium, total (SI: mmol/L and conventional mg/dL)
B-Red cell distribution width (fL)	S/P-Sodium (SI: mmol/L and conventional: mEq/L)
B-Red blood cell morphology	S/P-Blood urea nitrogen (SI: mmol/L and conventional: mg/dL)
	S/P-Phosphorous (SI: mmol/L and conventional: mg/dL)
Urinalysis (dipstick)	S/P-Bicarbonate (SI: mmol/L and conventional: mEq/L)
U-Hemoglobin/erythrocytes/blood	S/P-Glucose (mmol/L and mg/dL)

Table 10 Laboratory Safety Variables

Hematology/hemostasis (whole blood)	Clinical chemistry (plasma or serum)
U-Protein	S/P-Chloride (SI: mmol/L and conventional: mEq/L)
U-Microscopic analysis (if positive for blood, nitrites, or protein)	S/P-GGT (SI: µkat/L and conventional: U/L)
U-Glucose	
U-Ketones	
U-pH	
U-Specific gravity (ratio)	
U-Bilirubin	
U-Color	
U-Appearance	
U-Nitrites	
U-Leukocytes	
U-Urobilinogen	
U-Drugs of abuse, standard panel (Screening only)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, blood; GGT, gamma glutamyl transferase; P, plasma; S, serum; SI, International System of Units; TBL, total bilirubin; U, urine.

Additional Laboratory Assessments

Safety

- Serum calcitonin (pg/mL)
- Serum amylase (presented in both SI unit: µkat/L and conventional: U/L) and lipase (U/L)
- Coagulation parameters (prothrombin time [s], activated partial thromboplastin time [s], and international normalized ratio [INR] [ratio])
- MELD score (composite of INR, sodium, bilirubin, and creatinine)
- eGFR (mL/min/1.73 m^2) (Inker et al 2021)

Laboratory test results for hematology, coagulation, and clinical chemistry quantitative parameters below the lower limit of quantification for which the exact value cannot be determined, will be replaced with the 0.99 × LLOQ value. Similarly, laboratory test results above the upper limit of quantification (ULOQ) for which the exact value cannot be determined, will be replaced with 1.01 × the ULOQ value.

After the LLOQ/ULOQ replacement, change from baseline to each post-baseline visit for hematology, coagulation, clinical chemistry, MELD, and urinalysis quantitative parameters is defined as the post-baseline visit value minus the baseline value.

After the LLOQ/ULOQ replacement, hematology, coagulation, and clinical chemistry and quantitative parameters are also classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) based on the reference range indicator. Tables will utilize the LLOQ/ULOQ replacement. However, listings will display the original LLOQ/ULOQ inequality (eg, "< x" and "> x").

Potential Hy's Law

AST or ALT ≥ 3 × Upper Limit of Normal (ULN) together with TBL ≥ 2× ULN at any point during the study following the start of study intervention irrespective of an increase in ALP. Potential Hy's Law cases are determined without regard to the baseline value. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevation in transaminases and TBL must occur.

4.5.3.2 Presentations

Tables, graphs, and listings for laboratory data will be based on the on-study data only in the safety population and presented for each treatment group.

Laboratory test results for continuous clinical laboratory parameters will be summarized with n, mean, SD, median, minimum and maximum by treatment and analysis visit, and for change from baseline. Categorical parameters will be summarized by number and percentage of participants in each category by treatment and analysis visit. A frequency table will present number of participants reporting at least 1 treatment-emergent abnormality in chemistry, hematology, or coagulation clinical safety laboratory tests by highest category (Level 1 to 3, where Level 3 is the most extreme; refer to Appendix A for ranges). Low and high abnormalities for the same laboratory parameter will be summarized separately. Shifts from baseline to maximum value during the on-study period will be presented for urinalysis qualitative parameters.

Potential Hy's Law cases will be summarized by treatment and listed, and will be displayed for both the on-treatment and on-study periods. Maximum on-treatment ALT, AST, and TBL will be analyzed using categories described below and using baseline as defined in this document.

Participants with normal/near normal ALT (≤ 1.5 × ULN) at baseline:

- ALT < 3 × ULN and bilirubin not elevated (Non-Gilbert: Not elevated = total bilirubin < 2 × ULN. Gilbert: Not Elevated = direct bilirubin < 2 × baseline and INR ≤ 1.5)
- ALT < 3 × ULN and bilirubin elevated (Non-Gilbert: Elevated = total bilirubin ≥ 2 × ULN. Gilbert: Elevated = direct bilirubin ≥ 2 × baseline or INR > 1.5)
- ALT ≥ 3 × ULN and bilirubin not elevated
- ALT ≥ 3 × ULN and bilirubin elevated
- ALT ≥ 5 × ULN and bilirubin not elevated
- ALT ≥ 5 × ULN and bilirubin elevated
- ALT ≥ 8 × ULN and bilirubin not elevated
- ALT ≥ 8 × ULN and bilirubin elevated
- (repeat same categories with AST instead of ALT)

Participants with elevated ALT (> 1.5 × ULN) at baseline

- ALT < 2 × baseline and bilirubin not elevated (Non-Gilbert: Not elevated = total bilirubin < 2 × ULN. Gilbert: Not Elevated = direct bilirubin < 2 × baseline and INR ≤ 1.5)
- ALT < 2 × baseline and bilirubin elevated (Non-Gilbert: Elevated = total bilirubin ≥ 2 × ULN. Gilbert: Elevated = direct bilirubin ≥ 2 × baseline or INR > 1.5)
- ALT ≥ 2 × baseline and bilirubin not elevated
- ALT ≥ 2 × baseline and bilirubin elevated
- ALT ≥ 3 × baseline and bilirubin not elevated
- ALT ≥ 3 × baseline and bilirubin elevated
- ALT ≥ 5 × baseline and bilirubin not elevated
- ALT ≥ 5 × baseline and bilirubin elevated
- (repeat same categories with AST instead of ALT)

Evaluation of drug-induced serious hepatotoxicity (eDISH) plots of the maximum on-treatment (peak) TBL versus peak ALT or AST will be provided by treatment. Additionally, a cholestatic DILI screening plot will be provided plotting peak on-treatment TBL versus peak on-treatment ALP.

4.5.4 Vital Signs

4.5.4.1 Definitions and Derivations

Vital signs include SBP (mmHg), DBP (mmHg), heart rate (bpm), respiratory rate (breaths per minute), and temperature (°C). The mean of triplicate blood pressure measurements will be analyzed.

Additionally, vital signs values will be classified as normal (if value is within normal reference range), low (if value is below the normal reference range), and high (if value is above the normal reference range) according to the normal reference ranges (Table 11).

Table 11 Vital Sign Normal Reference Ranges

Parameter	Normal Reference Ranges
Systolic blood pressure	80 - 130 mmHg
Diastolic blood pressure	50 - 80 mmHg
Heart rate	50 - 100 bpm
Respiratory rate	12 - 20 breaths per minute
Temperature	≤ 37.0 °C

4.5.4.2 Presentations

Vital sign tables, graphs, and listings will be based on the on-treatment data only in the safety population and presented for each treatment group.

Vital sign results will be summarized with n, mean, SD, median, minimum, and maximum by treatment, and analysis visit and for change from baseline. A frequency table will present number of participants reporting at least 1 treatment-emergent abnormality (result outside of reference range). Low and high abnormalities for the same vital sign will be summarized separately. Observed values and change from baseline in SBP and heart rate measurements will be also presented in figures with mean and standard error of the mean.

All vital sign data will be listed. The listing will include reference ranges and classification of vital signs as normal, low, and high.

4.5.5 Electrocardiogram

4.5.5.1 Definitions and Derivations

Part A ECG evaluation includes:

- RR interval (msec)
- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)

- Heart rate (beats/min)
- QTcF interval (msec)
- Overall evaluation (normal, abnormal, borderline). If abnormal, reason and clinical significance are also collected.

ECGs will be performed in triplicate and the average of replicate measurements will be analyzed. Change from baseline is defined as the post-baseline visit value minus the baseline value.

Potentially clinically significant criteria for ECG parameters are as follows:

- QRS duration > 118 ms
- PR interval > 210 ms
- RR < 600 ms (resting heart rate > 100 bpm)
- RR > 1330 ms (resting heart rate < 45 bpm)

QTcF intervals are classified as:

- ≥ 450 msec
- ≥ 480 msec
- ≥ 500 msec

QTcF increases compared to baseline are classified as:

- ≥ 30 msec
- ≥ 60 msec

4.5.5.2 Presentations

ECG tables and listings will be based on the on-treatment data only in the safety population and presented for each treatment group. ECG parameters (except for the overall evaluation) will be summarized with n, mean, median, SD, minimum, and maximum, at each visit and for change from baseline.

Number and percentage of participants within each QTcF interval classes at any time during the on-treatment period will be also reported together with number and percentage of participants within QTcF increase classes at any time during the on-treatment period.

ECG parameters fulfilling potentially clinically significant criteria at any time during treatment will be summarized by treatment.

Overall evaluation will be analyzed as shift from baseline to last value in the on-treatment period.

5 TIMING OF ANALYSIS

Analysis will be conducted by the sponsor after final clinical data lock.

6 REFERENCES

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Appendix A Reference Ranges

Table A1 Reference Table for Abnormality Level Criteria Cutoffs, Chemistry

Parameter	Units	Low/High	Level 1	Level 2	Level 3
Sodium	mEq/L	Low	< 132	< 130	< 125
		High	> 150	> 155	> 160
Potassium	mEq/L	Low	< 3.6	< 3.4	< 3.0
		High	> 5.5	> 6.0	> 6.5
Chloride	mEq/L	Low	< 95	< 88	< 80
		High	> 108	> 112	> 115
Bicarbonate	mEq/L	Low	< 20	< 18	< 15
		High	N/A	N/A	>30
Blood urea nitrogen	mg/dL	High	> 23	> 27	> 31
Glucose, Fasting	mg/dL	Low	< 70	< 54	N/A
		High	≥ 100	≥ 126	N/A
Glucose, Random	mg/dL	Low	< 70	< 54	N/A
		High	N/A	≥ 200	N/A
Calcium	mg/dL	Low	< 8.4	< 8.0	< 7.5
		High	> 10.5	> 11.0	> 12.0
Phosphorous	mg/dL	Low	< 2.5	< 2.0	< 1.4
Albumin	g/dL	Low	< 3.1	< 2.5	< 2.0
Amylase	U/L	High	> 1.1 × ULN	> 1.5 × ULN	> 3.0 × ULN
Lipase	U/L	High	> 1.1 × ULN	> 1.5 × ULN	> 3.0 × ULN
Creatinine	mg/dL	Increase	≥1.5 × baseline	≥2.0 × baseline	≥3.0 × baseline
eGFR	mL/min/1.73m^2	Decrease	≥ 25% decrease from baseline	≥ 50% decrease from baseline	≥ 75% decrease from baseline
Alkaline Phosphatase	U/L	High	> 1.5 × ULN	> 2.0 × ULN	> 3.0 × ULN

eGFR, estimated glomerular filtration rate; N/A, not applicable; ULN, upper limit of normal.
A laboratory result will be considered Level 1 only if outside of the normal laboratory reference range.

Table A2 Reference Table for Abnormality Level Criteria Cutoffs, Hematology, and Coagulation

Parameter	Units	Low/High or Decrease/Increase	Level 1	Level 2	Level 3
WBC	10^9/L	Low	< 3.500	< 3.000	< 1.000
		High	> 10.800	> 13.000	> 15.000
Hemoglobin	g/dL	Decrease	N/A	decrease from baseline of > 1.5	decrease from baseline of > 2.0
		Increase	N/A	increase from baseline of > 2.0	increase from baseline of > 3.0
Hemoglobin (male)	g/dL	Low	≤ 13.5	< 12.5	< 10.5
Hemoglobin (female)	g/dL	Low	≤ 12.0	< 11.0	< 9.5
Platelets	10^9/L	Low	< 140	< 125	< 100
Lymphocytes	10^9/L	Low	< 1.000	< 0.750	< 0.500
		High	> 4.000	> 10.000	> 20.000
Neutrophils	10^9/L	Low	< 2.000	< 1.000	< 0.500
Eosinophils	10^9/L	High	> 0.650	> 1.500	> 5.000
Prothrombin Time	seconds	High	> 1.1 × ULN	> 1.3 × ULN	> 1.5 × ULN
Activated partial thromboplastin time	seconds	High	> 1.0 × ULN	> 1.21 × ULN	> 1.41 × ULN

N/A, not applicable; ULN, upper limit of normal; WBC, white blood cell.

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