Statistical Analysis Plan	
Official title:	A Phase II, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of CS0159 in the Treatment of Patients with Nonalcoholic Steatohepatitis (NASH)
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Statistical Analysis Plan

A Phase II, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of CS0159 in the Treatment of Patients with Nonalcoholic Steatohepatitis (NASH)

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Information described herein is confidential and may be disclosed only with the express written permission of the sponsor.

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Reviewers

The following reviews of the Statistical Analysis Plan (SAP) were conducted:

Name and Title	Role	Version Last Reviewed	Company / Organization
[redacted]			

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR_{AUC}	Accumulation ratio of AUC
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Under the concentration-time curve
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{0-\tau}$	Area under the concentration-time curve over a dosing interval
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration
AUDIT	Alcohol use disorders identification test
BLQ	Below limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
C4	7α-hydroxy-4-cholesten-3-one
CI	Confidence interval
CK-18	Cytokeratin-18
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
cT1	Iron-corrected t1
CV	Coefficient of variation
DBP	Diastolic blood pressure
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis

Abbreviation	Term
EOT	End of treatment
FAS	Full analysis set
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transferase
HDL-C	High-density lipoprotein cholesterol
HDL-P	High-density lipoprotein particle
HOMA	Homeostatic model assessment for insulin resistance
ICH	International Council for Harmonisation
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDL-P	Low-density lipoprotein particle
LFC	Liver fat content
LLOQ	Lower limit of quantification
LS	Least-squares
MAR	Missing at random
max	Maximum
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
MMRM	Mixed model repeated measures
MNAR	Missing not at random
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NC	Not calculated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
NIT	Noninvasive test
NR	No result
PD	Pharmacodynamics
PDFF	Proton density fat fraction
PK	Pharmacokinetic
PMM	Pattern-mixture model
PT	Prothrombin time
QD	Once daily
QTcF	Corrected QT interval by Fridericia
RDI	Relative dose intensity
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SI	International system of units
SOC	System organ class
$t_{1/2}$	Half-life
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures and listings
TG	Triglyceride
t_{max}	Time to maximum plasma concentration
WHO DD	World Health Organization Drug Dictionary

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	6 Dec, 2022	4.0
eCRF	28 September 2022	0.05

2. Protocol Details

2.1. Overall Study Design

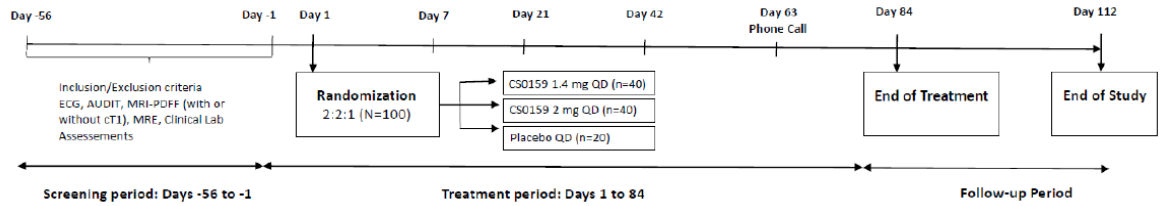
This will be a multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to evaluate the safety, tolerability, PK, and efficacy of CS0159 in the treatment of patients with nonalcoholic steatohepatitis (NASH) over 12 weeks.

Potential patients will be screened from Day -56 to Day -1 to assess their eligibility to enter the study. Imaging biomarkers noninvasive testing (NIT) will be performed through magnetic resonance imaging (MRI) proton density fat fraction (PDFF) and iron-corrected T1 (cT1), but no liver biopsy. Additionally, patients enrolled at a site with the capability to conduct magnetic resonance elastography (MRE) will have the option to undergo the MRE testing at the screening period and at Week 12 of this study.

Patients will be randomized in a 2:2:1 ratio using an interactive web response system (IWRS) to receive matching CS0159 1.4 mg or 2 mg, or placebo tablets QD, respectively. Randomization will be stratified by diabetes status. The diabetic patients will be evenly distributed among the patient groups.

On Day 1, the following assessments will be performed predose: physical examination, urine pregnancy test, vital signs, wet biomarkers, pharmacokinetics (PK) and pharmacodynamics (PD) assessments, and pruritus assessments (5-D Pruritus scale and Peak Pruritus Numerical rating scale).

There will be a total of up to 8 visits to the clinical site and 1 phone call visit on Week 9, including up to 2 screening visits; IWRS randomization on Day 1; and visits on Day 7 (Week 1), Day 21 (Week 3), Day 42 (Week 6), Day 63 (phone call at Week 9), and Day 84 (Week 12). A final safety follow-up visit will occur on Day 112 (Week 16).



Abbreviations: AUDIT = alcohol use disorders identification test; cT1 = iron-corrected T1; ECG = electrocardiogram; MRE = magnetic resonance elastography; N = number of patients; MRI-PDFF = magnetic resonance imaging proton density fat fraction; QD = once daily.

2.2. Study Objectives

2.2.1. Primary Objectives

Safety

- To evaluate the safety and tolerability of CS0159 in patients with NASH treated over 12 weeks.

Efficacy

- To assess the changes in liver steatosis through MRI-PDFF from baseline to Week 12.

2.2.2. Secondary Objectives

Pharmacokinetics (PK) and pharmacodynamics (PD)

- To assess the PK and PD profiles of CS0159.

Efficacy

- To assess the changes in inflammation in alanine aminotransferase (ALT) levels from baseline to Week 12.

2.2.3. Exploratory Objectives

- To explore the changes in liver steatosis, inflammation, and fibrosis through a set of target biomarkers from baseline to Week 12.
- To explore changes in inflammation through cT1 from baseline to Week 12.
- To explore the dose-response relationship of CS0159 on markers of hepatic steatosis, inflammation, and fibrosis in NASH from baseline to Week 12.
- To explore the dose-response relationship of CS0159 on metabolic markers.

2.3. Sample Size and Power

The sample size of 40 patients per active dose groups with 20 patients in placebo group would provide 80% statistical power under the following assumptions:

- $\alpha = 0.05$, 2-sided test
- Placebo mean % Δ from baseline in LCF = -10%, active mean % Δ from baseline in LCF = -25%
- Common standard deviation= 19%.

2.4. Primary Efficacy Endpoint

- The LFC as measured by MRI-PDFF mean changes from baseline to Week 12.

2.5. Secondary Efficacy Endpoints

- The proportion of patients with ≥30% reduction in liver fat through MRI-PDFF from baseline to Week 12.
- The ALT mean changes from the baseline to Week 12.
- The proportion of patients having a ≥30% reduction in ALT levels from the baseline to Week 12.

2.6. Safety Endpoints

- Incidence and severity of adverse events (AEs)/treatment-emergent AEs.
- Incidence and severity of adverse drug reactions.
- Clinical laboratory assessments (hematology, biochemistry, urinalysis, and hematopoietic and coagulation markers).

2.7. PK/PD Endpoints

Pharmacokinetics:

- Pharmacokinetic parameters of unchanged CS0159, including but not limited to the area under the concentration-time curve (AUC; $AUC_{0-\infty}$, AUC_{0-last}, $AUC_{0-\tau}$), maximum concentration (C_{max}), time to maximum plasma concentration (t_{max}), half-life ($t_{1/2}$), and accumulation ratio of AUC in plasma.

Pharmacodynamics:

- Plasma concentrations and PD parameters of the biomarkers of farnesoid X receptor (FXR) target engagement fibroblast growth factor 19 (FGF19) and serum 7α-hydroxy-4-cholesten-3-one (C4) from baseline to Week 12.

2.8. Exploratory Endpoints

The exploratory endpoints of the study are the mean changes from baseline to Week 12 in:

- Inflammatory and fibrosis biomarkers (alkaline phosphatase [ALP], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], platelet count, cytokeratin-18 [CK-18]), procollagen C3, and enhanced liver fibrosis (ELF, namely tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid).

- The proportion of patients with cT1 mapping ≥880 milliseconds (ms) at the baseline having a ≥80 ms reduction in cT1 levels.
- Metabolic biomarkers (fasting glucose, insulin, Homeostatic Model Assessment for Insulin Resistance [HOMA] index, hemoglobin A1c, and bile acids).
- Standard lipid panel (total cholesterol [TC], calculated low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TGs]).
- Lipid profile (nuclear receptor and metabolism-altering mechanisms of action).
- Insulin sensitivity index (lipoprotein insulin resistance index based on 6 lipoprotein parameters).
- Lipoprotein particle concentration and size including low-density lipoprotein particle (LDL-P) and high-density lipoprotein particle (HDL-P).
- GlycA and branched-chain amino acid concentrations.
- Bile acids profile (total), and C4 (an intermediate in the synthesis of bile acids from cholesterol and a biomarker of hepatic 7α-hydroxylase [CYP7A1] activity).

2.9. Potential Posthoc Analysis

- NIS-4 (NASHnext). Serum will be saved for potential posthoc analysis of NIS-4 changes from baseline to Week 12 after the last dose of study intervention.

3. Estimand(s)

The ICH[1] E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary objectives. Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of patients targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each patient that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

3.1. Estimands for the Primary Objectives

The main estimand is defined through the following five attributes:

3.1.1. Treatment Condition of Interest

The treatment conditions of interest are CS0159 1.4 mg administered daily, and CS0159 2 mg administered daily, and are compared with a matching placebo administered daily.

3.1.2. Population of Patients Targeted by the Clinical Question

The population targeted by the clinical question is adults with NASH as defined by the inclusion/exclusion criteria.

3.1.3. Variable Obtained from Each Patient Required to Address the Clinical Question

The variable to address the clinical question is the mean changes in LFC as measured by MRI-PDFF from baseline to Week 12.

3.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a treatment policy strategy.

The following table describes how intercurrent events will be collected and handled within the analysis.

Table 1 Handling of Intercurrent Events for the Primary Estimand

Intercurrent event	Data collection and analysis
• Premature treatment discontinuation	Patients will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.

Intercurrent event	Data collection and analysis
• Use of prohibited concomitant medication	
• Early withdrawal from study • Lost to follow-up • Death	These events will lead to missing values, and analyses will be performed with MMRM analysis assuming missing at random.

3.1.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the mean difference of change from baseline in LFC at Week 12 between treatment groups. A Mixed Model Repeated Measure (MMRM) model assuming missing at random (MAR) will be performed. The model will include treatment, visit, treatment-by-visit interaction and diabetes status (yes vs no) as fixed effects and the baseline LFC value as a covariate.

The LS means, 95% confidence interval (CI) for the LS means, difference between the LS means for each active treatment groups compared to placebo, 95% CI for difference, and P value will be presented for both absolute and percentage changes from baseline in LFC at Week 12.

3.1.6. Sensitivity Estimators for the Primary Estimand

A Pattern-Mixture Model implemented with multiple imputations will be performed as the sensitivity analysis, assuming missing not at random (MNAR) mechanism.

3.2. Estimands for the Secondary Objective

The main estimand is defined through the following five attributes:

3.2.1. Treatment Condition of Interest

The treatment conditions of interest are CS0159 1.4 mg administered daily, and CS0159 2 mg administered daily, and are compared with a matching placebo administered daily.

3.2.2. Population of Patients Targeted by the Clinical Question

The population targeted by the clinical question is adults with NASH as defined by the inclusion/exclusion criteria.

3.2.3. Variable Obtained from Each Patient Required to Address the Clinical Question

- Changes in inflammation in ALT levels from baseline to Week 12
- The proportion of patients with ≥30% reduction in liver fat through MRI-PDFF from baseline to Week 12

- The proportion of patients having a ≥30% reduction in ALT levels from the baseline to Week 12.

3.2.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a combination of treatment policy strategy and composite strategy.

The following table describes how intercurrent events will be collected and handled within the analysis.

Table 2 Handling of Intercurrent Events for the Secondary Estimand

Intercurrent event	Data collection and analysis
• Early withdrawal from study • Lost to follow-up • Death	• For continuous endpoints, analyses will be performed with MMRM analysis assuming missing at random. • For binary endpoints, patients have no efficacy assessments available on Week 12 will be consider as non-responder in line with the composite strategy.
• Premature treatment discontinuation • Use of prohibited concomitant medication	Patients will be followed and data collected after the intercurrent event will be used in analysis in line with a treatment-policy strategy.

3.2.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the comparison of estimated LS means of change from baseline in ALT levels and the differences in proportion of responders between treatment groups at Week 12.

The mean difference of change from baseline to Week 12 between treatment groups will be analyzed using a Mixed Model Repeated Measure (MMRM) model assuming missing at random (MAR). The model will include treatment, visit, treatment-by-visit interaction and diabetes status (yes vs no) as fixed effects, and the baseline ALT value as a covariate.

The LS means, difference between LS means for each active treatment groups compared to Placebo, the corresponding 95% CIs, and P value will be presented for both absolute and percentage changes from baseline in ALT levels at Week 12.

The differences in proportion of responders for each active treatment groups compared to Placebo will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusting by the diabetes status and baseline fibrosis stage. Patients with missing value at Week 12 will be considered as non-responders. The adjusted odds ratio, 95% CI for adjusted odds ratio and P value will be presented.

3.2.6. Sensitivity Estimators for the Secondary Estimands

For continuous endpoint, a Pattern-Mixture Models implemented with multiple imputations assuming MNAR mechanism will be performed as sensitivity analysis.

Sensitivity analysis for binary secondary endpoints will be performed using the same CMH test as the one used in the secondary efficacy analysis excluding patients with missing Week 12 data.

4. Analysis Populations

In accordance with ICH E3 and E9[3], the following analysis sets will be used for the analyses.

4.1. All Screened Set

The All Screened Set will include every patient who has signed the informed consent form. The All Screened Set will be used for summaries of disposition and the associated listing.

4.2. Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all randomized patients who had at least one dose of study treatment. Patients will be analyzed according to their randomized treatment. The FAS will be the study population used for the presentation of efficacy analyses.

4.3. Safety Analysis Set

All randomized patients who receive at least 1 dose of the study drug or placebo will be included in the Safety Analysis Set. Patients will be analyzed according to the treatment received. The SAS will be the study population used for presentation of safety information.

4.4. Pharmacokinetics (PK) Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized patients who receive an active study drug and who have any measurable plasma concentration of CS0159 for analysis. Patients will be analyzed according to the treatment actually received. The PK Analysis Set will be the study population used for presentation of PK information.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the date of first dose of study drug.

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

The date of the first dose of study drug for each patient will be taken from the CS0159 or Placebo Administration eCRF page. If the date in this eCRF page is missing, alternatively the date of randomization will be used.

The date of the last dose of treatment for each patient will be taken from the CS0159 or Placebo Administration eCRF page.

5.1.2. Screening/Baseline Period

Patients will undergo study-specific screening within 56 days prior to first administration of the study drug (Day 1). Patients will sign the study inform consent form in the presence of the investigator (or appropriate designee), prior to any screening procedures being performed.

Data collected at Day 1 prior to dosing will be considered as baseline values. If the measurement on Day 1 are not available, the last non-missing value collected before the first dose of study drug in the screening period will be used as the baseline value.

5.1.3. Treatment Period

Data collected at Day 1 following dose administration will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date of the first dose of study drug up to and including the date of the last dose of treatment.

5.1.4. Visit Windows

All data will be analyzed using nominal study visit as defined in the Study Schedule and eCRF. All study site visits, the follow-up visit, and required phone calls may be performed within a window of ± 2 days.

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

The handling of missing data for the primary and secondary efficacy endpoints is discussed in Section 3.1 and 3.2. With these exceptions, values for missing data will not be imputed unless specified.

5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications and Medical History

Missing and / or incomplete dates for medications, medical history and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of: the earliest possible start date, and the date of first dose of study drug.
- The latest possible start date.
- The latest possible stop date.

For a missing / incomplete stop date the later date of the following will be imputed:

- The earlier date of the latest possible stop date and the date of last dose of treatment.
- The earliest possible stop date.
- The earliest possible start date.

Here, the earliest possible date is defined as:

- The date itself if available.
- The date of the first day of the month, if month and year are available but the day is missing.
- The date of the first day of the year, if year is available but day and month are missing.
- The day of informed consent, if the date is completely missing.

The latest possible date is defined as:

- The date itself if available.
- The date of the last day of the month, if month and year are available but the day is missing.

- The date of the last day of the year, if year is available but day and month are missing.
- The date of last known date on the study for the patient plus one year, if the date is completely missing.

6. Statistical Methods

6.1. General Principles

All data processing, summarization and analyses will be performed using Labcorp Drug Development's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those patients with data.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of patients in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

In accordance with the baseline value definition in Section 5.1.2, the absolute and percentage change from baseline will be derived as follows:

Absolute change (unit) = post-baseline value – baseline value

Percentage change = [(post-baseline value– baseline value) / baseline value] × 100

All statistical comparisons will be made using two sided tests at the α=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided.

All laboratory test results will be received from the central laboratories, and the results will be provided in standard internal units. For the TFLs, the results will be summarized or presented in International System of Units (SI) units.

6.2. Patient Disposition and Data Sets Analyzed

Patients disposition will be summarized by treatment group and overall, where appropriate, for the All Screened Set. The following information will be reported:

- Number of patients for the following categories:
  - Screened
  - Screen failure
  - Reason for screen failure
- Number and percentage of patients for the following categories:
  - Randomized
  - Treated
  - Not treated

  - Complete the treatment
  - Discontinued the treatment
  - Reasons for treatment discontinuation
  - Completed the study
  - Discontinued the study
  - Reasons for study discontinuation
- Number and percentage of patients included in each study population

A patient will be regarded as having completed the study if the status recorded on the End of Study eCRF form is Complete, or assessments at the time of end of treatment (EOT) visit and follow-up have been completed. A patient will be considered as having discontinued the study if they have a eCRF status of premature study discontinuation.

A listing of all patients with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the All Screened Set.

A listing of all screen failed patients with their reasons for screen failure will be presented for the All Screened Set. A separate listing of patients who failed at least one inclusion / exclusion criteria including a text description of the criterion failed will be presented for the All Screened Set.

A listing of all randomized patients with their randomization details, including first dose date and time, and actual treatment received will be presented for the Full Analysis Set.

A listing of all patients excluded from at least one analysis set will be presented for the All Screened Set.

6.3. Protocol Deviations

All important protocol deviations will be summarized for the Full Analysis Set by treatment group and overall. The number of unique patients with at least one important protocol deviation as well as the number of patients in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all patients with one or more protocol deviations will be presented for the Full Analysis Set. In addition, a listing of the patients affected by Coronavirus Disease of 2019 (COVID-19) and the type of COVID-19 disruption will be provided for the Full Analysis Set.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the FAS by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at Baseline
- Weight (kg) at Baseline
- Body mass index (kg/m^2) at Baseline [calculated as (body weight / height^2) where weight is in kg and height is in m]
- Body Temperature (°C) at Baseline
- Respiration Rate (breaths/minute) at Baseline
- Systolic Blood Pressure (SBP [mmHg]) at Baseline
- Diastolic Blood Pressure (DBP [mmHg]) at Baseline
- Pulse Rate (beats/minute) at baseline

Total counts and percentages of patients will be presented for the categorical variables of:

- Age group (<= 65 years, > 65 to <= 75 years, > 75 years)
- Sex
- Race
- Ethnicity

Demographic characteristics will be listed for the FAS.

6.4.2. Baseline Characteristics

Baseline characteristics of importance will be summarized for the FAS by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate.

- Liver fat by MRI-PDFF
- Liver stiffness by MRE
- Iron-corrected T1
- Fibrosis stage
- Diabetes status

Additionally, important clinical laboratory evaluations at baseline are summarized below

Liver chemistry markers

- ALT
- AST
- GGT
- ALP

Metabolism markers

- Fasting glucose
- Fasting insulin,
- HOMA-IR (non-diabetic)

- HOMA-IR (diabetic)
- HbA1c, %
- TC
- LDL-C
- HDL-C
- TG

Fibrosis markers

- CK-18 (M65)
- Procollagen C3
- AST-to platelet ratio index
- ELF

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline characteristics will be listed for the FAS.

6.4.3. Medical History

Medical history is defined as any condition, with the exception of the study indication, that the patient may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study. See section 5.2.3 for imputation of missing or partial dates for medical history.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 25.0] and will be presented by System Organ Class (SOC) and Preferred Term (PT). The SOCs and PTs are to be sorted by Internationally Agreed order SOCs and descending PTs in the total column.

Medical history records will be summarized for the FAS by treatment group and overall as follows:

- The number and percentage of patients with at least one medical history record will be presented.
- The number and percentage of patients with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-patient and within-patient by medical history start date for the FAS.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version March 2022 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken within 6 months prior to screening with a stop date prior to the first dose date of study drug.
- Concomitant medications are those with a start date on or after the first dose date of study drug, or those with a start date before the first dose date of study drug and either a stop date on or after the first dose date of study drug, or are ongoing at the end of the study.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the FAS by treatment group and overall as follows:

- The number and percentage of patients with at least one prior / concomitant medication will be presented.
- The number and percentage of patients with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the FAS. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the first dose date of CS0159 and will be presented for those patients who received at least one dose of CS0159. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.5. Measurements of Treatment Compliance

Treatment compliance is defined as the number of tablets that were actually taken relative to the number of tablets that should have been taken as per the protocol for the duration of actual treatment exposure.

In general, the percentage overall compliance, assessed by tablet count, will be calculated as follows:

$$Compliance\ (\%) = \frac{(Number\ of\ tablets\ dispensed - Number\ of\ tablets\ returned)}{Number\ of\ days\ on\ treatment \times Number\ of\ tablets\ prescribed\ per\ day} \times 100\%$$

Number of days on treatment will be calculated as (last dose date - first dose date) +1

The calculated percentage compliance will be categorized as:

- < 80% compliance
- ≥ 80% compliance

Compliance will be summarized for the FAS by treatment group as follows:

- Percent compliance will be presented by default summary statistics.
- Number and percentage of patients within each of the compliance categories will be presented. Any patients with missing data will be presented as part of a "Missing" category.

Treatment compliance will be listed together with exposure for the FAS. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Efficacy

The main objective of the study is to assess the changes in liver steatosis through magnetic resonance imaging (MRI) proton density fat fraction (PDFF) from baseline to Week 12. All hypothesis tests will be 2-sided at the 0.05 level of significance unless otherwise stated.

6.6.1. Primary Efficacy Analysis

The primary efficacy variable is defined as change from baseline in LFC as measured by MRI-PDFF at Week 12.

The LFC measured by MRI-PDFF will be summarized using standard descriptive statistics by treatment groups at each visit, as well as the absolute and percentage changes from baseline.

The absolute and percentage changes from baseline in LFC value at Week 12 will be analyzed using a Mixed Model Repeated Measures (MMRM) method assuming missing data being missing at random (MAR). The unstructured covariance matrix will be used. The model will include treatment, visit, treatment-by-visit interaction, baseline fibrosis stage and diabetes status as fixed effects and baseline LFC value as a covariate. No imputation will be performed. All available data following randomization up to and including Week 12 will be included in the model. For patients who discontinued treatment, measurements made after treatment discontinuation will also be included in line with the treatment policy strategy.

The estimates of LSM and the LSM differences between CS0159 treated arm with placebo arm at Week 12 will be derived from the model. The corresponding 95% CIs and p value will also be derived from the model.

Test for normality of the response variable will be conducted. In cases normality assumption deemed unreasonably held, non-parametric test will be conducted, specifically, Wilcox rank sum test will be performed for comparisons of changes from baseline between each of the CS0159 treated arm with placebo arm.

LFC value will be additionally plotted against visits by line graphs to demonstrate its changes over time during the study period.

6.6.2. Sensitivity for the Primary Analyses

Sensitivity analysis will be performed using a Pattern-Mixture Model (PMM) with multiple imputation implementation without the assumption of MAR. Multiple imputation will be performed to impute values after patient's discontinuation from the trial based on "as treated" model (Little and Yau, 1996)[4]. Dropout patients will be considered as having zero active treatment exposure as treated when conducting the imputation. These unobserved values after dropout are therefore assumed to share similar disease progression or biomarker characteristics as those of the placebo control. This approach is expected to yield conservative treatment effect estimation than that of the MMRM with MAR assumption. The implementation of the PMM with the aforementioned approach is as follows:

1. Intermittent missing values will be imputed using a Markov Chain Monte Carlo (MCMC) method, in order to obtain a monotone missing data pattern, 500 imputation datasets will be generated.
2. Imputation of missing endpoint values under MNAR assumption, using complete data only from control group to impute unobserved endpoints.
3. Analysis with complete data after imputations. The MMRM model including treatment, visit, treatment-by-visit interaction, diabetes status, and baseline fibrosis stage as fixed effects and the baseline LFC value as a covariate will be performed. The analysis results of estimates and standard errors are saved.
4. Rubin's rule will be used to combine the analysis results in order to draw inference.

6.6.3. Secondary Efficacy Analysis

6.6.3.1. Change from Baseline to Week 12 in ALT

The ALT values will be summarized using standard descriptive statistics by treatment groups at each visit, as well as the absolute and percentage changes from baseline.

The absolute and percentage ALT changes from the baseline to Week 12 will be analyzed using the similar method as that of the primary efficacy endpoint. The MMRM model with unstructured covariance matrix will be performed, including treatment, visit, treatment-by-visit interaction, baseline fibrosis stage and diabetes status as fixed effects and baseline LFC value as a covariate. All observed data will be included in the model.

The estimates of LSM and the LSM differences between CS0159 treated arm with placebo arm at Week 12 will be derived from the model. The corresponding 95% CIs and p value will also be derived from the model.

Test for normality of the response variable will also be conducted. Wilcox rank sum test will be performed in cases normality assumption deemed unreasonably held.

ALT value will be additionally plotted against visits by line graphs to demonstrate its changes over time during the study period.

6.6.3.2. Proportion of patients with ≥30% reduction in liver fat through MRI-PDFF from baseline to Week 12

The differences in proportions of patients with ⩾30% reduction in liver fat through MRI-PDFF from baseline to Week 12 between the CS0159 treated arms and the placebo arm will be analyzed using a CMH model, adjusting for baseline fibrosis stage and diabetes status. Patients with missing MRI-PDFF data at Week 12 will be considered as non-responders. Point estimates of the proportions for each treatment arm will be provided along with the corresponding 95% CIs. Binomial proportion 95% CIs for proportions will be calculated using the Clopper-Pearson method. Adjusted odds ratio, 95% CI for adjusted odds ratio and p-values will be derived from the CMH model.

The number of responders and non-responders by treatment groups will be graphically presented with bar chart.

6.6.3.3. Proportion of patients having a ≥30% reduction in ALT levels from the baseline to Week 12

The differences in proportions of patients having a ⩾30% reduction in ALT levels from the baseline to Week 12 between the CS0159 treated arms and the placebo arm will be analyzed using a CMH model, adjusting for baseline fibrosis stage and diabetes status. Patients with missing ALT levels at Week 12 will be considered as non-responders. Point estimates of the proportions for each treatment arm will be provided along with the corresponding 95% CIs. Binomial proportion 95% CIs for proportions will be calculated using the Clopper-Pearson method. Adjusted odds ratio, 95% CI for adjusted odds ratio and p-values will be derived from the CMH model.

The number of responders and non-responders by treatment groups will be graphically presented with bar chart.

6.6.4. Sensitivity Analyses for the Secondary Efficacy Analysis

Similar sensitivity analysis for change from baseline in ALT levels will be performed as that of the primary efficacy endpoint. A Pattern-Mixture Models implemented with multiple imputations assuming MNAR mechanism will be performed.

Sensitivity analyses for binary efficacy endpoints will be performed by repeating the same CMH test as the one used in the secondary efficacy analysis excluding patients with missing Week 12 data.

6.6.5. Subgroup Analysis

Provided there are sufficient patients of at least 10 patients within a subgroup for any treatment group for statistical analysis, subgroup analyses will be conducted for the Primary Efficacy Analysis on the following:

- Diabetes status (yes vs no, where diabetes status will be removed as covariate)
- Sex (male vs female)
- Morbid Obesity (BMI $\geqslant$ 40 kg/m^2 vs others)
- Baseline fibrosis stage (F0/F1 vs F2/F3/F4, where baseline fibrosis stage will be removed as covariate)

6.6.6. Exploratory Analysis

Summaries of actual values, absolute and percentage changes from baseline to Week 12 will be presented for the following exploratory endpoints by treatment group using descriptive statistics for the FAS:

- Inflammatory and fibrosis biomarkers (ALP, AST, GGT, platelet count, CK-18), procollagen C3, and ELF (namely tissue inhibitor of metalloproteinases 1, amino-terminal propeptide of type III procollagen, and hyaluronic acid)
- The proportion of patients with cT1 mapping $\geqslant$880 ms at baseline having a $\geqslant$80 ms reduction in cT1 levels
- Metabolic biomarkers (fasting glucose, insulin, HOMA index, hemoglobin A1c, and bile acids)
- Standard lipid panel (TC, calculated LDL-C, HDL-C, and TGs)
- Lipid profile (nuclear receptor and metabolism-altering mechanisms of action)
- Insulin sensitivity index (lipoprotein insulin resistance index based on 6 lipoprotein parameters)
- Lipoprotein particle concentration and size including LDL-P and HDL-P
- GlycA and branched-chain amino acid concentrations

- Bile acids profile (total), and C4 (an intermediate in the synthesis of bile acids from cholesterol and a biomarker of hepatic CYP7A1 activity)

No formal statistical tests will be conducted.

The exploratory endpoints will be additionally plotted against visits by line graphs to demonstrate its changes over time during the study period.

A listing of all exploratory endpoints data including derived percentage change from baseline will be provided for the Full Analysis Set.

6.7. Safety

6.7.1. Extent of Exposure

Duration of exposure will be defined in days as:

Duration of exposure (days) = [date of last dose – date of first dose] + 1 – off-treatment days

Off-treatment days will be calculated as the sum of days that patient did not take any study drug.

The calculated exposure duration of exposure will be categorized as:

- less than 7 days
- >= 7 days to < 21 days
- >= 21 days to < 42 days
- >= 42 days to < 63 days
- >= 63 days to < 84 days
- >= 84 days

Duration of exposure will be summarized in two ways for the Safety Analysis Set by treatment group and overall.

- Descriptive statistics will be presented for duration of exposure.
- Number and percentage of patients within each of the exposure categories will be presented.

The following exposure parameters will be summarized for the Safety Analysis Set by treatment group and overall:

- Total dose prescribed (mg) will be calculated as number of days on treatment × planned daily dose [number of days on treatment will be calculated as (last dose date of CS0159 - first dose date of CS0159) + 1]
- Total dose taken (mg) will be calculated as (number of tablet dispensed – number of tablet returned) × planned daily dose
- Percent of expected doses taken will be calculated as [(total dose taken) / (total dose prescribed)] × 100%

- Relative dose intensity (RDI) will be calculated as [(total dose taken / number of days on treatment) / planned daily dose] × 100%

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together with compliance for the Safety Analysis Set. Further, study treatment administration data will be listed for the Safety Analysis Set.

6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 25.0]. Adverse event related definitions in this study are as follows:

- TEAEs are either events with start date on or after the first dose of study drug, or events with start date prior to the first dose of study drug whose severity worsens on or after the date of first dose of study drug.
- Treatment-emergent serious AEs (TESAEs) will be defined as TEAEs regarded by the investigator as Serious Event = "Yes".
- The relationship between a TEAE and treatment is assessed as related, possibly related, unlikely related, or not related. Unknown/missing relationship will be considered as related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related or possibly related to treatment or with unknown / missing relationship to treatment.
- Assessment of AE severity will be based on the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE[5], version 5.0).
- Liver events (eg, suspected drug-induced liver injury or liver toxicity), will be included as AEs of special interest in this study.

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the Safety Analysis Set by treatment group and overall as follows:

- An overview of TEAEs including the number and percentage of patients with at least one of each mentioned TEAE type:
  - Any TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
    - TEAEs by maximum severity
    - TEAEs with severity grade ≥ 3
  - Any treatment-related TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any treatment-emergent serious AE (TESAE)
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any treatment-related TESAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any TEAE of special interest

- The number and percentage of patients reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
  - TEAEs
  - Treatment-related TEAEs
  - TEAEs leading to death
  - TEAEs of special interest
  - TEAEs by maximum severity
  - TEAEs by relationship with treatment
  - TEAEs with severity grade ≥ 3 by relationship with treatment
  - TEAEs leading to discontinuation of study treatment by relationship with treatment
  - TESAEs
  - Treatment-related TESAEs
  - TESAEs by relationship with treatment

In the above summaries, patients with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included in the counts of the 'Number of Patients with at least one TEAE', 'System Organ Class' and 'Preferred Term' rows of the summary but they will not be included in the counts by severity.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie PTs will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed as recorded in eCRF for the Safety Analysis Set. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the date of first dose of study drug. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of serious TEAEs
- Listing of TEAEs leading to discontinuation of study treatment
- Listing of TEAEs leading to death
- Listing of TEAEs of special interest

6.7.3. Laboratory Evaluations

Data for the following hematology, biochemistry, coagulation and urinalysis analytes received from central laboratory are to be measured at the scheduled visits indicated in the Schedule of Assessments in protocol. An example table which serves as reference is provided below, based on specifications in the protocol appendix 2.

Table 3 Laboratory Tests

Hematology	Biochemistry	Coagulation

• Hemoglobin
• Hematocrit
• White Blood Cell Count
• Red Blood Cell Count
• Platelet count
• Reticulocyte count
• Differential WBC count (absolute)
  ○ Neutrophils
  ○ Lymphocytes
  ○ Eosinophils
  ○ Basophils
  ○ Monocytes
	• Albumin
	• ALT
	• ALP
	• Amino-terminal propeptide of type III procollagen
	• Amylase
	• AST
	• Bile acids
	• BUN
	• Calcium
	• Chloride
	• Creatine kinase
	• Creatinine
	• Cytokeratin-18 (M65)
	• Direct bilirubin
	• eGFR
	• Fasting glucose
	• GGT
	• Globulin
	• Glucose
	• GlycA
	• HDL-C and HDL-P
	• Hemoglobin A1c
	• HOMA index
	• Hyaluronic acid
	• Insulin
	• Insulin sensitive index
	• LDH
	• LDL-C and LDL-P
	• Magnesium
	• Metalloproteinases 1
	• NIS-4
	• Potassium
	• Procollagen C3
	• Sodium
	• Total cholesterol
	• Triglycerides
	• Uric acid
	• Total bilirubin
		• Fibrinogen
		• International normalized ratio
		• Partial thromboplastin time
		• Prothrombin time
		Urinalysis
		• Protein
		• Glucose
		• Ketones
		• Blood
		• Specific gravity
		• pH
		• Bilirubin
		• Leukocytes
		• Urobilinogen
		• Nitrite
		• Urine red blood cells
		• Urine while blood cells

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl transferase; HDL-C = high-density lipoprotein cholesterol; HDL-P = high-density lipoprotein particle; HOMA = homeostatic model assessment for insulin resistance; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle

All laboratory data will be reported in International System of Units (SI) units. All quantitative laboratory test values at each assessed visits will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous variables for the Safety Analysis Set by treatment group and overall as follows:

- Observed values and absolute change from baseline at each assessed visit for each standard continuous laboratory parameter
- Number and percentage of patients with categorized shift (low, normal and high) values relative to the reference range at baseline compared to each post-baseline visit

Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed.

Listings of all clinical laboratory data including derived change from baseline will be provided for the Safety Analysis Set. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L).

The summary tables will include data from scheduled visits only, while data from unscheduled visits will not be included in summaries but will be listed.

6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (beats/min);
- respiration rate (breaths/min);
- body temperature (℃).

Observed values and absolute change from baseline for each vital sign parameter will be summarized by treatment group and visit for the Safety Analysis Set.

A listing of all vital signs data including derived change from baseline will be provided for the Safety Analysis Set.

The summary tables will include data from scheduled visits only, while data from unscheduled visits will not be included in summaries but will be listed.

6.7.5. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken during the study:

- An overall investigator assessment classified as normal, abnormal, not clinically significant / abnormal, clinically significant
- Heart rate (beats/min);
- RR interval (ms);
- PR interval (ms);
- QRS interval (ms);
- QT interval (ms);
- Fridericia corrected QT (QTcF) interval (ms);

The maximum post-baseline QTcF values will be classified in accordance with the ICH E14[6], Boundaries as presented in Table 4.

Table 4 QTcF Interval ICH E14 Boundaries

QTcF Interval	Criteria (msec)
Observed QTcF interval	<=450 ms >450 to <=480 ms >480 to <=500 ms >500 ms
Change from baseline in QTcF interval	<=30 >30 to <= 60 ms >60 ms

The ECG findings will be summarized by treatment group and overall for the Safety Analysis Set as follows:

- Observed values for each ECG parameter at each assessed visit using default summary statistics for continuous variables
- A categorical summary of QTcF classification according to ICH E14 boundaries will be provided using counts and percentages for baseline and maximum post-baseline value
- Counts and percentages of patients within each of the ECG interpretation categories (normal; abnormal, not clinically significant; abnormal, clinically significant) at each assessed visit

A listing of all ECG data including derived change from baseline will be provided for the Safety Analysis Set.

The summary tables will include data from scheduled visits only, while data from unscheduled visits will not be included in summaries but will be listed.

6.7.6. Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History or AEs as appropriate and will be listed and summarized as such [See Sections 6.4.3 (Medical History) and 6.7.2 (Adverse Events)].

For each physical examination body system, the number and percentage of patients within each abnormalities category (abnormal, not clinically significant/ clinically significant) at

baseline and at each assessed visit will be summarized by treatment group and overall for the Safety Analysis Set.

Physical examination findings (normal / abnormal) and details of abnormalities will be listed for each patient at each assessed visit.

The summary tables will include data from scheduled visits only, while data from unscheduled visits will not be included in summaries but will be listed.

6.7.7. Other Safety Variables

Other safety variable such as: pregnancy test, pruritus assessments will be listed only.

6.7.8. Data Monitoring

Safety data in addition to PK and PD data will undergo formal review by an independent DMC who will meet at least once and ad hoc as needed and will be responsible for the oversight of overall safety of the study. They will receive unblinded data but strictly firewalled (except for the unblinded DMC support staff who are also firewalled) and barred from sharing any information with anyone else including Labcorp and sponsor personnel and will make recommendations on continuation or discontinuation of the study and/or modifications to continue the study.

There will be a DMC Charter to govern how the DMC will operate and will include details regarding safety data that will be reviewed such as AEs, SAEs, as well as safety labs such as chemistry, hematology, urinalysis, thyroid, lipid, and liver.

In addition, the DMC and the sponsor will have a low threshold to call an ad hoc meeting if there is emerging AE or safety data that raises a potential concern. The DMC are explicitly required to meet if any of the potential stopping rule cases occur as described in section 4.4.1 of the protocol.

The DMC will also review the primary efficacy endpoint, mean changes in LFC (measured by MRI-PDFF) from baseline to Week 12, patients treated with active doses compared to the change from baseline in patients treated with placebo. Furthermore, DMC will review the PK/PD analysis outcomes and provide a recommendation for the study.

6.8. Pharmacokinetic Assessments

Whole blood samples will be collected for measurements of the plasma concentration of CS0159 at specified time points as defined in the Schedule of Assessments in protocol.

6.8.1. Pharmacokinetic Analysis

Non-compartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin® (Version 8.1 or higher).

Plasma concentrations of CS0159 and plasma PK parameters will be listed and summarized for each assessed visit and scheduled timepoint (if applicable) by treatment group for the PK Analysis Set.

Summary statistics for plasma concentrations and the following PK parameters will include n, mean, standard deviation (SD), coefficient of variation (% CV), median, minimum, maximum, geometric mean and geometric coefficient of variation (% geo CV).

Parameter	Definition
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration
$AUC_{0-\tau}$	Area under the concentration-time curve over a dosing interval
C_{max}	Maximum plasma concentration
t_{max}	Time of the C_{max}
$t_{1/2}$	Apparent terminal elimination half-life
AR_{AUC}	Accumulation ratio of AUC

Additional PK parameters may be determined where appropriate.

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be the observed values obtained directly from the concentration-time profiles. For multiple peaks if any, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

Regression-related PK parameters (λ_z Lower, λ_z Upper, λ_z N, R^2-adj, λ_z and λ_z Span Ratio) will not be included in summary tables, but will be listed separately from other PK parameters.

6.8.1.1. Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows:

- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If a predose concentration of first dosing is missing, these values may be set to zero by default.

6.8.1.2. Criteria for the Calculation of Apparent Terminal Elimination Half-Life

- Number of Data Points

  At least three data points will be included in the regression analysis and preferably should not include Cmax.

- Goodness of Fit

  When assessing terminal elimination phases, the adjusted R^2 value will be used as a measure of the goodness of fit of the data points to determine the λ_z, the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.

  Regression-based parameters will only be calculated if the adjusted R^2 value of the regression line is greater than or equal to 0.7.

- Period of Estimation

  The time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives.

Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

6.8.1.3. Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- For any partial AUC determination (i.e. AUC over a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the pharmacokineticist.

- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 30% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be presented but excluded from descriptive statistics.

- AUC values will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.

6.8.1.4. Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- Positive predose value(s) of first dosing greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

6.8.2. Presentation of Pharmacokinetic Data

All PK concentration and parameters will be summarized by treatment group, assessed visit and scheduled timepoint (only for concentration data) in tabular formats. Concentration and PK parameter values except t_{max} will be summarized by nominal sampling time using descriptive statistics including: n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric coefficient of variation

(geo %CV). Summary statistics for t_{max} include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum and maximum. The plasma concentrations will be analyzed by nominal time and PK parameters will be analyzed by assessed visit. Actual times will be used for individual concentration-time plots.

The arithmetic mean of concentrations of CS0159 will be presented graphically on both linear and semi-logarithmic scales as mean ± SD for each treatment group by visit. For individual profiles, figures will be presented for each patient with concentration-time profiles on both linear and semi-logarithmic scales. Concentration values of 0 will not be plotted in the semi-logarithmic plots. The following figures will be produced:

- Individual concentration versus actual time
- Arithmetic mean concentration versus nominal time

All PK concentrations and parameters will be listed.

For presentation of plasma concentration data, the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is no result (NR) or nonreportable concentration values, these will be set to missing.
- If all the values are BLQ, then the arithmetic mean, SD, coefficient of variation, median, min and max will be presented as 0, and the geometric mean and geometric %CV will be denoted as NC.
- If there are less than three values in the data series, only the min, max, n and n (BLQ) will be presented. The other summary statistics will be denoted as not calculated (NC).
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as 0 and the geometric mean and geometric %CV will be denoted as NC.
- Out-of-window blood samples will be excluded from the calculation of descriptive statistics.

For presentation of PK parameters, the following rules will apply:

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

- The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

If there are less than three values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as not calculated (NC).

6.9. Pharmacodynamics Analysis

PD biomarkers including plasma fibroblast growth factor 19 (FGF19) and serum 7α-hydroxy-4-cholesten-3-one (C4) will be listed and summarized for the FAS.

Observed values, absolute and percentage changes from baseline at each assessed visit for each pharmacodynamic biomarker will be presented by treatment group using standard descriptive statistics.

7. Changes in the Conduct of the Study or Planned Analysis

There were no changes in the conduct of the study at the time of preparing this SAP. Any deviations from the approved SAP will be described and justified in the CSR.

8. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, 3Jan2023	Final version 1.0
Version 2.0, 17Feb2023	Added contents to SAP text section 6.8. Thus this section no longer refers to external PK analysis plan. Minor changes: Replace “plasma” with “serum” 7α-hydroxy-4-cholesten-3-one (C4).

9. References

[1] ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at https://database.ich.org/sites/default/files/E9_Guideline.pdf

[2] ICH. *Addendum on Estimands and Sensitivity Analysis in Clinical Trials*, Guideline E9(R1). Available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[3] ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[4] Little, R., Yau, L. *Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs*. Biometrics, 1996, vol. 52, 1324-1333.

[5] *Common Terminology Criteria for Adverse Events (CTCAE) v6.0. Available at* https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60

[6] ICH. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*. 12 May 2005. Available at https://database.ich.org/sites/default/files/E14_Guideline.pdf