NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

PLATFORM

CADPT02A12001 / NCT04147195

NASH EXploratory Single and COmbination Treatment (NEXSCOT): An open label, multicenter, platform study to evaluate the safety, tolerability, pharmacokinetics and efficacy of various single and combination treatments in patients with non-alcoholic fatty liver disease (NAFLD) who manifest a non-alcoholic steatohepatitis (NASH)-like biomarker phenotype

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Amendment 1 Final

Release date: 09-Feb-2022

Number of pages: 27

Commercially Confidential Information (CCI)

Commercially Confidential Information

Commercially Confidential Information

Table of contents

List of tables

Commercially Confidential Information

List of figures

1 Introduction

1.1 Scope of document

The Reporting Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CADPT02A12001".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

Tables, Figures, Listings (TFL) detail the presentation of the data, including shells of summary tables, figures and listings, and Programming Datasets Specification **(**PDS) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Study reference documentation

Final study protocol, version v04, 02 Jun 2021 and final SOM, version v02, 17 Aug 2021 are available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives and related endpoints

1.3.1 Primary objective(s) and related endpoints

Primary objective	Endpoints related to primary objective
To determine the safety and tolerability of single or combination therapy during 12 weeks of treatment.	Safety endpoints (including vital signs, physical examination, laboratory measurements, ECG); Adverse events.

1.3.2 Secondary objective(s) and related endpoints

Secondary objective(s)	Endpoints related to secondary objectives
To determine the effect of single or combination therapy on circulating markers of ongoing liver fibrosis	Enhanced Liver Fibrosis (ELF) Test
To determine the effect of single or combination therapy on intrahepatic lipid content	Percent (%) liver fat as measured by Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF)
To determine the effect of single or combination therapy on cardiometabolic risk parameters	Body weight, waist and hip circumference, waist-to-hip ratio, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1c (HbA1c), fasting glucose, fasting insulin, fasting lipid profile
To determine the effect of single or combination therapy on circulating markers of liver and/or systemic inflammation	Liver function test (ALT), high-sensitivity C reactive Protein (hsCRP)

To evaluate the pharmacokinetics (PK) of each individual agent when administered as a single or combination therapy.	Plasma concentrations

Commercially Confidential Information

1.4 Study design and treatment

This is a non-confirmatory, multicenter, open label, platform study in NAFLD patients with a NASH-like biomarker phenotype to examine the effects of single and combination therapies over 12 weeks of treatment.

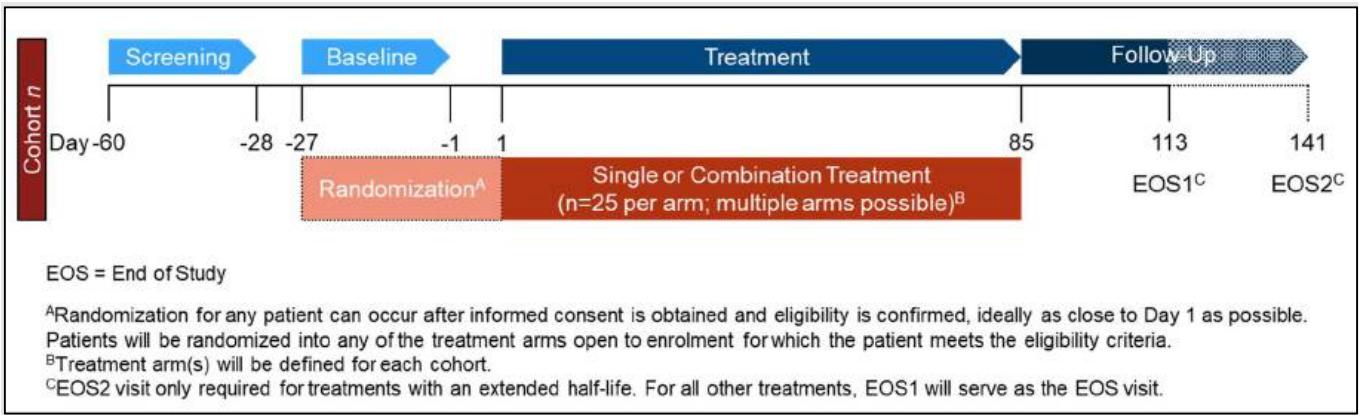
Commercially Confidential Information

Commercially Confidential Information

There is a maximum of five cohorts planned. Each cohort will consist of a 33-day screening period (Day -60 to Day -28), a baseline period of 27 days (Day -27 to Day -1), a treatment period of 12 weeks (Day 1 to Day 85), and a study completion evaluation (End of Study [EOS] 1) approximately 28 days after the last drug administration (Day 113). CCI

Participants will be advised to maintain their recommended diet for NAFLD during the study. The study design scheme is shown below in Figure 1-1:

Figure 1-1 Study design



2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial at each IA and at the end of study (CSR).

The study FIR template (mock slides) can be found in CREDI in the study RAP folder.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

3 Interim analyses

Commercially Confidential Information

Commercially Confidential Information

4 Statistical methods: Analysis sets

The **safety analysis set** will include all participants that received any study drug.

The **PK analysis set** will include all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The **efficacy/PD analysis set** will include all participants with available efficacy/PD data and no protocol deviations with relevant impact on efficacy/PD data.

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

Throughout this document, 'treatment' refers to the treatment arm of a cohort that each participant is assigned to.

For treatments with an extended half-life, EOS1 will be required as a standard, non-EOS post-treatment follow up visit, and EOS2 will serve as the EOS visit. For all other treatments, EOS1 will serve as the EOS visit. If a participant discontinues study treatment early, the participant should be scheduled for a subsequent visit at which time all assessments at the EOS1 visit should be performed. For treatments with an extended half-life, if a participant discontinues

early after EOS1, then the participant should be scheduled for a subsequent visit at which time all assessments at the EOS2 visit should be performed.

The Day 113 (EOS1) visit for treatments with no extended half-lives and the Day 141 (EOS2) visit for treatments with extended half-lives will be pooled and reported/analyzed together under a common EOS visit, labeled as 'EOS', in the reporting/analysis. The Day 113 (EOS1) visit for treatments with extended half-lives will be reported/analyzed as a distinct visit, labeled as 'Day 113', in the reporting/analysis.

For the End of Study (EOS) visit, only data from study completers will be included in the efficacy summary/analysis tables/figures. Safety summary/analysis tables/figures will include data from all participants, i.e., both study completers and non-study completers for the End of Study (EOS) visit.

4.1 Cohort-specific information:

4.1.1 Cohort 1:

Cohort 1 will evaluate the use of LYS006 alone and tropifexor (LJN452) in combination with LYS006 for the treatment of elevated liver fat, liver inflammation and liver fibrosis in NAFLD participants who manifest a NASH-like biomarker phenotype. The drug combination of LYS006 and tropifexor (LJN452) may provide clinical benefit beyond that of either drug alone, considering different, complementary mechanisms of action of these drugs.

Approximately 50 participants will be randomized in a 1:1 ratio to one of the following treatment arms:

- Treatment arm 1: LYS006 Commercially Confidential Information
- Treatment arm 2: Tropifexor (LJN452) Commercially Confidential Information + LYS006 Commercially Confidential Information

The treatments used in cohort 1 (i.e. LYS006 and Tropifexor) do not have extended half-lives, so the EOS1 visit will serve as the end-of-study visit for participants randomized to any of the two treatment arms of cohort 1 (i.e. for all cohort 1 participants).

4.1.2 Protocol deviation codes

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Participants are excluded from safety analysis in case of these PDs:		Exclude participant from safety analysis set
INCL01	*Written informed consent must be obtained prior to screen procedures*	

Category Deviation code	Text description of deviation	Data exclusion
Participants are excluded from PK analysis in case of these PDs:		Exclude participant from PK analysis set
INCL01	Written informed consent must be obtained prior to screen procedures	
OTH13	*Additional data collected is not as per effective ICF/ Protocol requirement*	Exclude only the PK data that the protocol deviation relates to from the visit the protocol deviation occurred on
Participants are excluded from efficacy/PD analysis in case of these PDs:		Exclude participant from efficacy/PD analysis set
INCL01	Written informed consent must be obtained prior to screen procedures	
OTH12	*Follow up end of study MRI was not completed within 7 days of treatment discontinuation*	Exclude participant from imaging data analyses from the visit the protocol deviation occurred on (for imaging data, visit can be either Day 85 or EOS)
OTH13	*Additional data collected is not as per effective ICF/ Protocol requirement*	Exclude only the efficacy/PD data that the protocol deviation relates to from the visit the protocol deviation occurred on
COMD01	*Following randomization initiation of new antidiabetic, insulin, betablockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, thyroid hormone, psychotropic, estrogen, birth control*	Exclude participant from all efficacy/PD analyses from the protocol deviation's study day (i.e., prohibited medication's start day) onwards

Category Deviation code	Text description of deviation	Data exclusion
TRT03	*Treatment modification guidelines per protocol not followed*	Exclude participant from all efficacy/PD analyses from the protocol deviation's study day onwards – PD is exclusionary only under specific criteria*

**TRT03 PD is exclusionary if dose interruption is > 2 days and/or decreased dose is continued for > 2 weeks.*

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

All participants within the PK analysis set will be included in the PK data analysis.

For participants with protocol deviations affecting the PK analyses, the data will be excluded as described in Table 4-1 above.

The evaluation of the pharmacokinetics (PK) of each individual agent when administered as a single or combination therapy is one of the secondary objectives of this study.

5.1 Variables

PK samples will be collected in all participants at the visits defined in the Assessment schedule (see protocol section Table 8-1).

Each study drug will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) and method specifics will be listed in the central laboratory manual.

Concentrations will be expressed in mass per volume units and will refer to the free base.

Commercially Confidential Information

PK parameters will be determined using the actual recorded sampling times and noncompartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher). Cmax, Tmax, AUC0-t and other parameters as appropriate will be estimated and reported from the plasma concentration-time data if feasible.

5.2 Descriptive analyses

Plasma concentration data will be listed by cohort, treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point.

Summary statistics per analyte, per time point will be reported. Summary statistics will include sample size (n), mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum

Commercially Confidential Information

The geometric mean and its CV will not be reported if the data includes zero values.

The concentration data may be integrated with data from other studies for population PK analysis in the future and will be reported separately.

Pharmacokinetic parameters will be listed by cohort, treatment and participant. Pharmacokinetic parameters will be summarized by treatment and visit. Summary statistics will include sample size (n), mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where sample size (n), median, minimum and maximum will be presented. A geometric mean will not be reported if the data set includes zero values.

5.2.1 Graphical presentation

Arithmetic mean (SD) plasma concentration by time will be plotted on linear-linear scale (all treatments in the same graph).

Overlaying individual plasma concentration by time profile, by treatment will be plotted (one graph per treatment, all participants in the same graph) on linear-linear scale.

Individual plasma concentration by time profile, by participant will be plotted on linear-linear scale (one graph per treatment and participant).

5.3 Statistical model, assumptions and hypotheses

Commercially Confidential Information

An unstructured variance-covariance structure will be used. If the unstructured covariance causes model convergence issues, then other simpler covariance structures will be considered in the following sequence: TOEP, AR(1) and CS. The least squares mean differences between treatments and the associated 2-sided 90% confidence intervals in the logarithmic scale will be obtained at each visit and will then be back-transformed to the original scale to produce the geometric mean ratio (GMR) between treatments and associated 90% CIs at each visit and for each PK parameter. The associated p-value will also be obtained at each visit and for each PK parameter.

6 Statistical methods for Efficacy/Pharmacodynamic (PD) parameters

All participants within the efficacy/PD analysis set will be included in the efficacy/PD data analysis.

Data will be excluded from the efficacy/PD analyses in the following cases:

- For participants with protocol deviations affecting the efficacy/PD analyses, the data will be excluded as described in Table 4-1 above.
- For participants that discontinued treatment early, the following *programming rule* will be applied: *Any efficacy assessments that occurred on or after the treatment discontinuation study day, will be excluded from all efficacy/PD data analyses. An exception to this is the Day 85 visit or EOS visit imaging data (MRI and MRE assessments), that will be excluded only if they occurred prior to study day 56 (i.e., imaging assessments that occurred on or after study day 56, will not be excluded from the imaging analyses).*
- Participants with <80% treatment compliance

Treatment compliance calculation

For each subject, the treatment compliance (%) will be calculated using the following formula:

$$100 * \left(\frac{Number\ of\ capsules\ expected\ to\ be\ taken\ up\ to\ the\ last\ treatment\ day\ -\ Number\ of\ capsules\ missed\ during\ the\ treatment\ period}{Number\ of\ capsules\ expected\ to\ be\ taken\ up\ to\ the\ last\ treatment\ day}\right)$$

where,

Number of capsules expected to be taken up to the last treatment day =
last treatment day * CCI , if treated with LYS006

OR

last treatment day * CCI , if treated with LJN452

Number of capsules missed during the treatment period =
Sum (Number of capsules expected to be taken in the dosing modification period x - Number of capsules actually taken in the dosing modification period x)

Notes:

- The treatment compliance will be calculated separately for each treatment (LYS006 and LJN452).
- The last treatment day is defined as the last available start or end treatment day, as reflected in the dosing dataset.

- A dose modification period is a period with either a dose change or a dose interruption. These periods will be identified in the dosing dataset under records with TYPE OF CHANGE='DOSE CHANGED' and TYPE OF CHANGE='DOSE INTERRUPTED', respectively.

- For the dose modification periods:

  - Only the dosing records with non-missing dose administered, non-missing start date and non-missing end date will be considered in the calculations.

  - Dose administered = Number of capsules administered

  - The number of capsules expected to be taken in a dosing modification period =

    (period end day – period start day +1) * CCI , if treated with LYS006

    OR

    (period end day – period start day +1) * CCI , if treated with LJN452

  - The number of capsules actually taken in a dosing modification period = (period end day – period start day +1) * dose administered

  - The frequency of dose administered will not be considered in the calculations, only the dose administered itself.

6.1 Primary efficacy objectives

There are no primary efficacy objectives for this study.

The primary objective of this study is related to the safety and tolerability of single or combination therapy during 12 weeks of treatment and is described in Section 8.

6.2 Secondary efficacy objectives

The secondary efficacy objectives are:

1. To determine the effect of single or combination therapy on circulating markers of ongoing liver fibrosis
2. To determine the effect of single or combination therapy on intrahepatic lipid content
3. To determine the effect of single or combination therapy on cardiometabolic risk parameters
4. To determine the effect of single or combination therapy on circulating markers of liver and/or systemic inflammation.

6.2.1 Variables

The secondary efficacy variables/endpoints related to the secondary efficacy objectives are:

1. Markers of liver fibrosis:
    - Enhanced Liver Fibrosis Test (ELF Test™):
        - Hyaluronic acid (HA)
        - Tissue inhibitor of metalloproteinases (TIMP-1)
        - Amino-terminal pro-peptide of procollagen type III (PIIINP)
2. Magnetic Resonance Imaging (MRI):
    - Percent (%) liver fat as measured by Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF)
3. Cardiometabolic risk parameters:
    - Body weight
    - Waist circumference
    - Hip circumference
    - Waist to hip ratio
    - Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)
    - Hemoglobin A1c (HbA1c)
    - Fasting glucose
    - Fasting insulin
    - Fasting lipid profile:
        - Total cholesterol
        - HDL-cholesterol
        - LDL-cholesterol
        - Triglycerides
        - Lipoprotein A
4. Liver function tests and liver and/or systemic inflammation markers:
    - Alanine aminotransferase (ALT)
    - High-sensitivity C-reactive Protein (hsCRP)

Baseline definition:

Baseline for ALT is defined as the mean of the last 2 non-missing measurements taken prior to the first dose of study drug administered at the Day 1 visit.

For all other secondary efficacy endpoints, baseline is defined as the last non-missing measurement prior to the first dose of study drug administered at the Day 1 visit.

All assessments (scheduled and unscheduled) will be considered into the derivation of the baseline.

6.2.2 Descriptive analyses

The raw measurements, the change from baseline measurements and the percentage change from baseline measurements of the above secondary efficacy endpoints will be listed by cohort, treatment, participant and visit/time.

Descriptive statistics will be provided for the raw measurements, the change from baseline measurements and the percentage change from baseline measurements of the above secondary efficacy endpoints by treatment and visit/time and will include sample size (n), mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum Commercially Confidential Information The geometric mean and its CV will not be reported if the data includes non-positive values. For the change from baseline data summary, the geometric mean and its CV will be based on log-transformed ratio to baseline (i.e., change from baseline in the log scale).

In addition, the proportion of participants with at least 30% relative reduction and 5% absolute reduction in % liver fat (i.e. percentage change from baseline <= -30% and change from baseline <= -5% respectively) will be tabulated separately by treatment.

6.2.2.1 Graphical presentation

Arithmetic mean (+/- SE) of the raw measurements, the change from baseline measurements and the percentage change from baseline measurements of the above secondary efficacy endpoints will be plotted over time and by treatment (all treatments in the same graph). In addition, geometric mean (+/- 80% CI) of the raw measurements and the ratio to baseline measurements of the above secondary efficacy endpoints will be plotted over time and by treatment (all treatments in the same graph).

Overlaying individual (spaghetti) plots of the raw measurements, the change from baseline measurements and the percentage change from baseline measurements of the above secondary efficacy endpoints will be provided over time and by treatment (one graph per treatment, all participants of each treatment in the same graph).

6.2.3 Statistical model, assumptions and hypotheses

A mixed-effect model for repeated measures (MMRM) analysis will be conducted for log-transformed ratio to baseline in ELF Test and ALT.

Commercially Confidential Information

An unstructured variance-covariance matrix will be used to account for correlation among multiple measurements from the same participant and variance heterogeneity. If the unstructured covariance causes model convergence issues, then other simpler covariance structures will be considered. Least squares mean, the associated 2-sided 80% confidence interval and the p-value will be obtained for each treatment at each visit and back transformed to the original scale, meaning that the least squares means will be expressed as geometric means after the back-

transformation on the original scale. Contrasts assessing trend over time will be constructed for each treatment using various functional forms as needed. Both cohort-wise and combined cohort analysis will be performed as appropriate.

Log-transformed ratio to baseline in % liver fat, hsCRP, HOMA-IR, HbA1c, fasting glucose, fasting insulin and fasting lipid profile as well as change from baseline in ELF Test, ALT and % liver fat, waist circumference, hip circumference, waist to hip ratio and percentage change from baseline in body weight will also be analyzed. Parameters with more than one post-treatment measurement will be subjected to the same MMRM analysis described above for ELF Test and ALT using untransformed baseline in lieu of log-transformed baseline as a covariate for the untransformed data analysis.

Commercially Confidential Information

Additionally, a multivariate ANCOVA will be done for the three-dimensional endpoint: log-transformed ratio to baseline in ELF Test, ALT and % liver fat at Week 12. The model will include treatment and stratification factor (race and BMI group at baseline) as classification factors and log-transformed baseline as a covariate. An arbitrary 3 by 3 covariance matrix will be assumed for the three-dimensional endpoint.

If there are sufficient data, then a subgroup analysis (ANCOVA) in participants with baseline liver fat >=10% will be performed to compare % liver fat between treatments.

Commercially Confidential Information

Baseline participant characteristics will be monitored closely and compared across cohorts to assess population drift which may occur because of improved general care and enrollment of either less or more healthy participants over time. The population drift, if present, will be accounted for using a modeling approach as appropriate.

6.2.3.1 Handling of missing data

Missing data will not be imputed for the univariate MMRM analysis. Assuming data is missing at random, a participant with missing value at a visit will still contribute to the estimation of the treatment effect at that particular visit as the likelihood-based MMRM borrows information from non-missing values of this participant and other participants.

For the Week 12 multivariate ANCOVA, an additional analysis with the last post-treatment observation carried forward for missing ELF Test and ALT values may be performed.

6.2.3.2 Graphical presentation of results

Not applicable.

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

7 PK/PD relationships

The relationships between individual PK profiles or derived PK parameters and various efficacy/PD measurements or derived variables (including, but not limited to ELF Test, ALT and % liver fat) may be explored using graphical approaches (e.g., scatter plots) and regression analysis as appropriate. Similarly, the relationship between % liver fat reduction and ALT reduction vs weight loss as well as ALT decrease vs % liver fat reduction may be explored as needed.

8 Statistical methods for safety and tolerability data

The primary objective of this study is to determine the safety and tolerability of single or combination therapy during 12 weeks of treatment.

All participants within the safety analysis set will be included in the safety data analysis.

For participants with protocol deviations affecting the safety analyses, the data will be excluded as described in Table 4-1 above.

8.1 Variables

All safety data collected including adverse events, body height, body weight, BMI, vital signs (blood pressure, pulse rate and body temperature), ECG intervals (PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF and QTcB), laboratory measurements (Hematology, Chemistry, Urinalysis, Coagulation and Pregnancy Test), as well as participant demographics, baseline characteristics, relevant medical history, current medical conditions, concomitant medications and significant non-drug therapies, and treatment information.

8.2 Descriptive analyses

Participant demographics and other baseline characteristics

All data for demographic and other baseline characteristics including disease characteristics (including but not limited to age, gender, race, ethnicity, country, height, weight, BMI, ALT, AST, GGT, hepatic fat fraction (%) and ELF) will be listed by cohort, treatment and participant. Summary statistics will be provided by treatment. Categorical data will be presented as frequencies and percentages. For continuous data, sample size (n), mean (arithmetic), SD, median, minimum and maximum will be presented. For selected parameters, the 25^{th} percentile (Q1) and 75^{th} percentile (Q3) will also be presented.

Relevant medical histories and current medical conditions at baseline will be listed by cohort, treatment, participant, system organ class (SOC) and preferred term (PT).

Treatment

Data for study drug administration (rescue medication) will be listed by cohort, treatment and participant.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by cohort, treatment, participant and the Anatomical Therapeutic Chemical (ATC) classification system.

Vital signs

All vital signs data will be listed by cohort, treatment, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time and will include sample size (n), mean (arithmetic), SD, median, 25^{th} percentile (Q1), 75^{th} percentile (Q3), minimum and maximum.

ECG evaluations

All ECG data will be listed by cohort, treatment, participant, and visit/time, and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time and will include sample size (n), mean (arithmetic), SD, median, 25^{th} percentile (Q1), 75^{th} percentile (Q3), minimum and maximum.

Clinical laboratory evaluations

All laboratory data will be listed by cohort, treatment, participant, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting

all parameters in a participant with any abnormal values. Summary statistics will be provided by treatment and visit/time and will include sample size (n), mean (arithmetic), SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum.

Adverse events

All information obtained on adverse events will be listed by cohort, treatment and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication, or present prior to start of treatment but increased in severity based on preferred term, or changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period) will be summarized in the following ways:

- by treatment, primary system organ class (SOC) and preferred term (PT).
- by treatment, primary system organ class (SOC), preferred term (PT) and maximum CTCAE grade.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

8.2.1 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vital signs, ECG intervals and laboratory measurements) will be created by treatment.

8.3 Statistical model, assumptions and hypotheses

Formal statistical analysis will not be performed on the safety and tolerability data. The statistical evaluation of all safety and tolerability data will be descriptive.

Commercially Confidential Information

Commercially Confidential Information

10 Derivations

10.1.1 HOMA-IR

Depending on the units which fasting glucose and fasting insulin are given in, HOMA-IR will be calculated as:

HOMA-IR = [Fasting glucose (mmol/L) x (fasting insulin (pmol/L)/6)] / 22.5

HOMA-IR = [Fasting glucose (mg/dL) x fasting insulin (uIU/mL)] / 405

Reference: https://www.thebloodcode.com/homa-ir-calculator/

Commercially Confidential Information

where age is given in years, BMI in kg/m^2, platelets in $10^9/L$, albumin in g/dL.

11 SAP deviations from protocol

Commercially Confidential Information

2. In the study protocol V03 sections 12.5.1 and 12.6, the model used for analyzing secondary CCI parameters with more than one post-treatment measurement is named as *'repeated measures analysis of covariance (ANCOVA)'*, whereas in the current SAP sections 6.2.3 and 6.3.3 it is named as *'mixed-effect model for repeated measures (MMRM)',* since this is a more appropriate wording for this model.

3. In the study protocol V03 section 8.5.1.1, it is stated that: *'A 100 mm visual analogue scale (VAS) will be used to assess the severity of participants itch (ranging from 0 = no itch at all to 10 = the worst imaginable itch).'*. However, 100 is the correct VAS value corresponding to the worst imaginable itch, so in the current SAP section 6.3.1 this has been corrected accordingly to *'100 = the worst imaginable itch'*.

12 Reference list

1. Clinical Trial Protocol, CADPT02A12001, Protocol Version 04, dated 02 Jun 2021.
2. Site Operations Manual, SOM Version 02, dated 17 Aug 2021.