Document Title:	Statistical Analysis Plan		
Version Number:	1.0	Date:	31 Mar 2020
Protocol Number:	SARO.17.004	Sponsor Name:	Zydus Discovery DMCC

A Phase 2, Prospective, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Saroglitazar Magnesium 2 mg and 4 mg in Patients with Non-alcoholic Steatohepatitis

Statistical Analysis Plan
(SARO.17.004)

Version 1.0 (Final)

31 MAR 2020

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1. INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from SARO.17.004 study. This document is based on protocol version 2.0, dated 02 August 2018. The statistical planning and conduct of analysis of the data from this study will follow the principles defined in relevant International Council for Harmonisation (ICH)-E9 guidelines. This Statistical Analysis Plan (SAP) has been developed prior to database lock or final analysis. Any changes from the planned analysis as described in the protocol are detailed here, and any differences described here supersedes the analysis presented in the protocol. Any deviations from the planned analyses described in this SAP will be documented in the clinical study report, together with the reason for such changes.

Prior to start of any statistical analyses, the database must be authorized and all decisions regarding assignment of patients to study populations must be completed. In addition, protocol deviations must be identified prior to the start of statistical analyses.

2. STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

Primary Objective

The primary objective of this study is to evaluate the changes in Non-alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) at week 24 from baseline and with no worsening of fibrosis in Non-alcoholic Steatohepatitis (NASH) patients.

Secondary Objectives

The secondary efficacy objectives of this study are:
- To evaluate the percentage of responders in the treatment groups.
- To evaluate the percentage of responders, defined as the disappearance of steatohepatitis over the time period up to Week 24 in patients treated with Saroglitazar Magnesium 2 mg and 4 mg.

- Changes from baseline to Week 24 in Saroglitazar Magnesium 2 mg and 4 mg for the following parameters:
  - Stage of steatosis, lobular inflammation and ballooning
  - Stage of fibrosis
  - Liver function tests (ALT, AST, ALP, GGT, Direct bilirubin, Total proteins and Albumin).
  - Lipids profile parameters (TG, TC, sdLDL, HDL, LDL, VLDL, non-HDL, ApoA1 and ApoB)
  - Insulin resistance and glycemic control parameters (FPG, HbA1c, Fasting insulin, C-peptide, Adiponectin, HOMA-B and HOMA-IR).
- To assess the safety of Saroglitazar Magnesium 2 mg and 4 mg in patients with non-alcoholic steatohepatitis over 24 weeks of treatment.

2.2 Study Description

2.2.1 Study design

This is a Phase 2 randomized, multi-center, double-blind, placebo-controlled proof of concept study to evaluate the safety and efficacy of Saroglitazar magnesium 2 mg and 4 mg in patients with NASH meeting pre-specified inclusion/ exclusion criteria. Male and female patients aged 18 to 75 years will be enrolled in this study. Approximately 15 patients who meet the inclusion and exclusion criteria will be enrolled.

Liver biopsy will be performed at the screening visit to confirm the diagnosis of NASH and to record the baseline NAFLD Activity Score. The histological evidence of NASH is defined as NAS ≥ 4 with a minimum score of 1 for all of its three components [steatosis, hepatocyte ballooning and lobular inflammation].

This study will be conducted over a period of up to 32 weeks and will include a 4-week screening phase, a 24-week treatment phase and a safety follow-up visit, 4 weeks after the last treatment. The study plan is provided below.
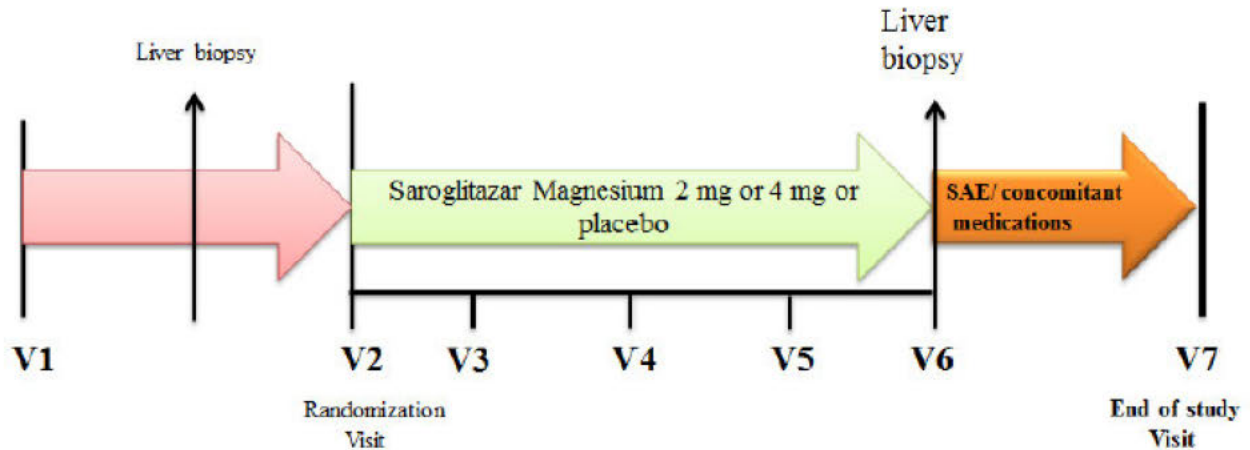
NOTE: Liver biopsy showing NASH within 6 months preceding Visit 1 can be used.

The study visits are planned at screening [-4 Week (-28 days)], Baseline/Enrollment Visit (Day 1± 7 days), Week 6 (Day 43 ± 7 days), Week 12 (Day 85 ± 7 days), Week 18 (Day 127 ± 7 days), Week 24 (Day 169/ ± 7 days) and a safety follow-up visit at Week 28 (Day 197 ± 7 days). All patients will be advised to follow a stable lifestyle. No change in the intensity of lifestyle (Diet/Exercise) will be allowed during the study period.

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2.2.2 Study plan

2.3   Randomization

An independent statistician will generate the randomization schedule(s) for study treatment assignment. Eligible patients will be randomized in a 2:2:1 ratio to receive Saroglitazar 2mg, Saroglitazar 4 mg or placebo. Block randomization will be performed. The block randomization schedule will be generated to ensure the treatment balance by using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA).

2.4   Blinding and Unblinding

The patients, investigators and all members of the Clinical Study team will be blinded to the treatment assignments while the study is in progress. Furthermore, the randomization scheme will not be available to the clinic staff, study monitors and/or other individuals. All study drug will be supplied in identical packages and study drug kits. The study drug tablets will be similar in color, smell, taste and appearance to maintain adequate blinding of evaluators. Neither the investigator nor the patient should be able to identify the received treatment. Unblinding of the treatment code will be done when all data have been verified, validated and the database is locked.

A sealed copy of the randomization code provided under separate envelope will be retained at the investigational site or as per applicable requirements. If the treatment code needs to be broken in the interest of patient safety, the Investigator is encouraged to contact an appropriate study Sponsor representative prior to unblinding if there is sufficient time. Depend on the individual circumstances (ie, medical emergency), the code may be broken prior to contact with the Sponsor. The study Sponsor must be informed in all cases in which the code was broken and of the circumstances involved. Additionally, the Sponsor may be required to unblind the patient if adverse event meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) to fulfill expedited regulatory reporting requirements. The event of unblinding will be documented in the source notes.

2.5   Treatments

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Study Treatment Name	Treatment Abbreviation on TFL	Treatment Order on TFL
Saroglitazar Magnesium 4 mg	Saroglitazar 4 mg	1
Saroglitazar Magnesium 2 mg	Saroglitazar 2 mg	2
Placebo	Placebo	3

2.6 Interim Analysis

No interim analysis is planned for this study.

3. ANALYSIS POPULATIONS

Subject evaluability and their impact on analysis populations will be determined prior to locking the database.

3.1 Efficacy Analysis Populations

The modified intent-to-treat (mITT) population includes all randomized patients who receive at least one dose of study drug and have at least one post-baseline visit. The mITT population will serve as the primary population for all efficacy analyses. Last observation carried forward (LOCF) method will be used as an imputation method for the efficacy variables with missing observations.

The supportive analysis of the primary and secondary efficacy endpoints will be conducted using the per-protocol population (PP). The PP population includes all randomized patients who meet all eligibility criteria, completed the study in compliance with the protocol, and do not have any CSR reportable protocol deviation that affects the evaluation of the efficacy endpoints.

The number of patients excluded from mITT and PP populations and a listing of excluded subjects from each analysis population with reason for exclusion will be presented. Any inconsistencies in key study results between mITT and PP populations will be examined and discussed in the clinical study report.

3.2 Safety Analysis Population

The safety population includes all randomized patients who receive at least one dose of study drug.

4. SAMPLE SIZE AND POWER CALCULATIONS

No formal sample size estimation was performed. This proof of concept study will include approximately 15 evaluable patients randomized in a 2:2:1 ratio to receive Saroglitazar Magnesium 2 mg (6 patients), Saroglitazar Magnesium 4 mg (6 patients) and placebo (3 patients).

5. PATIENT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Disposition of Patients

Patient disposition table will be based on all enrolled subjects who are consented to participate in the study. The following summaries will be included in the disposition table: total number of subjects screened in the study, number of subjects who failed screening, number of subjects randomized, number of subjects who completed the study, and number and percentage of subjects who discontinued from the study with reason for discontinuation. Percentages will be based on the number of subjects who are randomized. In addition, the number of subjects included in each analysis population (mITT, PP and Safety) will be presented separately.

Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized based on the mITT, PP and Safety populations.

Descriptive summaries will be provided for the demographic and baseline characteristics. Demographic characteristics such as age, gender, race, ethnicity, height, weight and Body Mass Index (BMI) will be summarized and tabulated for all the analysis populations. All the continuous variables (i.e., age, height etc.) will be summarized by n, mean, standard deviation, minimum, median and maximum values. All the categorical variables (i.e., gender) will be summarized as count and percentage. All demographic and baseline characteristics will be presented in data listings.

Medical history, previous and concomitant therapies

Medical history information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®, version 21.0 or higher). A summary will be provided including the frequency and percentage of subject with medical history terms by System Organ Class and Preferred Term for the Safety population. A by-subject listing of medical history information will be provided for all enrolled subjects including current and past diseases.

Prior therapies are the therapies/medications with stop date prior to first dose of study drug. Any therapy/medication usage at or post first dose of study drug is considered concomitant therapy.

All medications recorded during the study will be coded using the World Health Organization (WHO) Drug Dictionary (version DDEBSEP16). A summary will be provided for the

frequency and percent of subjects who had previous therapies/medications and a separate summary of subjects who had concomitant therapy/medications. Summaries will be based on the Safety population and will be by Anatomical Therapeutic Chemical (ATC) classification level 3 term and Preferred Name.

A listing of all prior and concomitant medications including the reported term, Preferred Name, ATC level 3 term, start dates, stop dates and other relevant data will be provided for all enrolled subjects.

6. EFFICACY ANALYSIS STRATEGY

6.1   General Considerations

Categorical variables will be summarized with the frequency and percentage of subjects in each category. Continuous variables will be summarized descriptively with the number of subjects, mean, standard deviation, minimum, median and maximum values. Change from baseline will be summarized similarly, but also with standard error. The change from baseline will be calculated as follows:

Change from baseline = Post baseline value – Baseline value

Percent Change = (Post baseline value – Baseline value) / Baseline value * 100.

The SAS® software (version 9.4) will be used for all analyses.

Decimal Precision

Unless otherwise noted, mean, median, standard deviation, minimum and maximum will be presented to two decimal places, percentage and confidence interval will be presented to one decimal place; and p-values will be presented to four decimal places.

Missing Date Procedures

Adverse events with completely missing dates will be considered treatment emergent. Medications with completely missing end dates will be considered concomitant. Adverse events and medications with partially missing start or end dates will be considered treatment-emergent and concomitant respectively unless the non-missing portion of the dates definitively proves otherwise.

For example, if a subject starts treatment on 20FEB2016, then adverse events with onset dates of FEB2016, 2016, or 05DEC would all be considered treatment-emergent, while

onsets dates of 2015 or JAN2016 would not be considered treatment-emergent. Medications starting or ending in FEB2016 or 2016 would be considered concomitant, medications ending in JAN2016 or 2015 would not.

6.2   Efficacy Endpoints

Primary Efficacy Endpoint:

The primary efficacy endpoint is the changes in NAFLD Activity Score (NAS) at Week 24 from baseline with no worsening of fibrosis.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are:

- Percentage of patients with decrease from baseline in NAFLD activity score by at least 2 point spread across in at least 2 of the NAS components (steatosis, hepatocyte ballooning, and lobular inflammation) at Week 24 with no worsening of fibrosis
- Percentage of patients with disappearance of steatohepatitis at Week 24.
- Change from baseline in stage of steatosis, lobular inflammation and ballooning at Week 24.
- Change from baseline in stage of fibrosis at Week 24.
- Change from baseline in liver function tests parameters (ALT, AST, ALP, GGT, Direct bilirubin, Total proteins and Albumin) at Week 24.
- Change from baseline in lipid profile parameters (TG, TC, sdLDL, HDL, LDL, VLDL, non-HDL, ApoA1 and ApoB) at Week 24.
- Changes from baseline in glycemic control and insulin resistance parameters (FPG, HbA1c, Fasting insulin, C-peptide, Adiponectin, HOMA-B and HOMA-IR) at Week 24.

6.3   Efficacy Hypotheses

This is a proof of concept study and no formal hypothesis testing will be conducted.

6.4   Statistical Methods for Efficacy Analyses

This is a proof of concept study with a small number of patients enrolled. All primary and secondary efficacy endpoints will be summarized descriptively by treatment as per section 6.1 for both mITT and PP populations.

Fisher's exact test will be used to compare the treatment differences for following endpoints in Saroglitazar 2 mg and Saroglitazar 4 mg treatment groups with placebo.

- Percentage of patients with decrease from baseline in NAFLD activity score by at least 2 point spread across in at least 2 of the NAS components (steatosis, hepatocyte ballooning, and lobular inflammation) at Week 24 with no worsening of fibrosis.

- Percentage of patients with disappearance of steatohepatitis at Week 24.

  Disappearance of steatohepatitis is defined as:

  (i) resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score (or)

  (ii) improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis).

  Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for Steatosis.

Two-sample t-test will be used to compare the treatment differences for the following endpoints in Saroglitazar 2 mg and Saroglitazar 4 mg treatment groups with placebo.

- Change from baseline in stage of steatosis, lobular inflammation and ballooning at Week 24.

- Change from baseline in stage of fibrosis at Week 24.

- Change from baseline in liver function tests parameters (ALT, AST, ALP, GGT, Direct bilirubin, Total proteins and Albumin) at Week 24.

- Change from baseline in lipid profile parameters (TG, TC, sdLDL, HDL, LDL, VLDL, non-HDL, ApoA1 and ApoB) at Week 24.

- Changes from baseline in glycemic control and insulin resistance parameters (FPG, HbA1c, Fasting insulin, C-peptide, Adiponectin, HOMA-B and HOMA-IR) at Week 24.

In addition to the descriptive summaries, treatment differences and 95% confidence for the treatment differences will be provided. All p-values presented are for the descriptive purpose only.

6.5   Sensitivity Analysis

A sensitivity analysis to explore the robustness of the efficacy results with respect to the protocol deviations will be performed using Per-Protocol population for the primary and secondary efficacy endpoints.

6.6 Subgroup Analyses and Effect of Baseline Factors

Due to the small sample size, no subgroup analysis is planned for this study.

6.7 Multiplicity Strategy

Not applicable.

6.8 Handling of Missing Data

Clarifications, wherever possible, will be obtained from the respective investigator for any missing data or for any illegible entry, unused or unauthenticated data. Subjects are required to have at least one post-baseline visit to be included in the mITT population. Last Observation Carried Forward (LOCF) will be used for the imputation of post-baseline missing values. Baseline values will not be carried forward for the imputation of missing values. Patients discontinued from study will be excluded from the PP population.

7. SAFETY ANALYSIS STRATEGY

Safety analyses will be conducted using the safety population on a treatment-emergent basis.

7.1 Safety Endpoints

The safety endpoints are:

- Frequency and Severity of Adverse events.
- Vital Signs (Systolic BP, diastolic BP, pulse rate, oral temperature and respiratory rate)
- Clinical laboratory testing (hematology, clinical chemistry and urinalysis)
- Twelve-lead electrocardiogram (ECG)
- Physical Examination.
- Body weight

7.2 Safety Hypothesis

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of the safety endpoints listed in Section 7.1.

7.3 Statistical Methods for Safety Analysis

Unless otherwise stated, the analysis population for all safety analysis is the safety analysis population as defined in Section 3.2.

7.3.1 Extent of Exposure

Study duration is defined as the date of last visit minus date of informed consent date plus one. Treatment duration is defined as the date of last dose minus the date of the first dose plus one. If the date of last dose is not available, the date of the last visit will be used in the calculation. If the date of first dose is not available, the date of baseline visit will be used in the calculation. Study duration and the treatment duration will be summarized descriptively.

Treatment compliance is calculated as the total number of tablets taken divided by the expected number of tablets to be taken during the study period multiplied by 100. Treatment compliance will be summarized descriptively. In addition, a categorical summary of compliance will also be presented using the following categories: < 80% 80% to 120% and >120%. A subject's is considered to be compliant, if he/she takes 80% to 120% of the study drug during the study period.

7.3.2 Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol section 9.4. A treatment-emergent AE (TEAE) is an event not present prior to exposure to study drug or any pre-existing event that worsens following exposure to study drug. The period for treatment-emergent AE analysis starts from the first exposure to the study drug until the patient exits the study. Adverse events (AEs) will be coded using MedDRA to give a preferred term and a SOC term for each event.

Descriptive summaries (frequencies and percentages) for specific TEAEs will be presented by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA Version 19.1) dictionary. In addition to an overall presentation of all TEAEs, reports will be generated for special classes of TEAEs such as study drug related TEAEs, serious TEAEs, Maximum severity and TEAEs resulting in treatment discontinuation. These reports will be supported by individual patient listings, as necessary.

Adverse events will be counted by the number of events as well as the number of patients. For the summaries which count the number of patients, multiple TEAEs with the same MedDRA preferred term within the same subject will only be counted once.

Only patient listings will be provided for AEs that occur after signing informed consent but prior to exposure to investigational product. These listings will comprise all events occurring during this period in any subject who consented to participate in the study.

These listings will at least contain but not limited to information such as onset and resolution times, maximum severity, causal relationship to study treatment and action taken.

7.3.3 Vital Signs

Vital signs parameters include blood pressure, pulse rate, oral temperature and respiratory rates. Vital signs assessments will be performed at screening, baseline, Week 6, Week 12, Week 18, Week 24 and Week 28 visits.

Descriptive summaries (N, mean, median, standard deviation, minimum and maximum values) of absolute (measured) values and change from baseline in each vital sign parameter at each scheduled assessment visit will be presented. A by-patient listing will be provided for all vital sign parameter results (scheduled and unscheduled) for all enrolled patients.

7.3.4 Physical Examination

Physical examination assessments will be performed at screening, baseline, Week 6, Week 12, Week 18, Week 24 and Week 28 visits. A by-patient listing will be provided for all physical examination parameter results (scheduled and unscheduled) for all enrolled patients.

7.3.4 Laboratory Results

Clinical laboratory assessments will be performed at screening, baseline, Week 6, Week 12, Week 18, Week 24 and Week 28 visits. Laboratory values will be presented using the International System of Units (SI units). Clinical laboratory evaluations consist of hematology, clinical biochemistry and urinalysis.

Absolute (measured), absolute (change) and relative (percent change) from baseline values will be summarized descriptively (N, mean, median, standard deviation, minimum, and maximum values) at each assessment for hematology and biochemistry parameters. A summary table of the categorical grade shift changes using the normal ranges from baseline to last study visit will be provided.

For summary purposes, each value below/above the limit of quantification (LOQ) will be imputed numerically to the nearest value below/above the limit, respecting the same number of digits than numerical values (e.g. if the number of digit=0, subtract/add 1 to the limit of quantification; if the number of digit =1, subtract/add 0.1 to the LOQ, etc).

A by-patient listing will be provided for all patients with laboratory results (scheduled and unscheduled). In addition, a listing of all clinically significant abnormal values will be provided.

7.3.5 ECG

A 12-lead electrocardiogram (ECG) will be performed at Screening, Baseline, Week 12, Week 24 and Week 28 visits. Investigator interpretation of ECG results (normal, abnormal clinically insignificant, abnormal clinically significant) will be summarized by treatment. A by-patient listing will be provided for all patients with ECG results (scheduled and unscheduled).

8. REFERENCES

Not applicable

9. LIST OF ABBEVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoA1	Apo lipoprotein A1
ApoB	Apo lipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BP	Blood pressure
CSR	Clinical study report
ECG	Electrocardiogram
FPG	Fasting plasma glucose
GGT	Gamma glutamyltransferase
HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein
HOMA-B	Homeostasis model assessment beta
HOMA-IR	Homeostasis model assessment for insulin resistance
ICH	International council for harmonisation
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Non-alcoholic steatohepatitis
PP	Per-protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sdLDL	Small dense low-density lipoprotein
SI	International System of Units
TEAE	Treatment Emergent Adverse Events
TC	Total cholesterol
TG	Triglyceride-cholesterol
VLDL	Very low-density lipoprotein
WHO	World Health Organization