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Document Title:	Statistical Analysis Plan		
Version Number:	1.0	Date:	31 Dec 2021
Protocol Number:	SARO.17.010	Sponsor Name:	Zydus Therapeutics Inc.

A Phase 2A, Single Center, Open-Label, Single-Arm, 24-week Study to Evaluate the Safety, Tolerability and Efficacy of Saroglitazar Magnesium 4 mg in Liver Transplant Recipients with Nonalcoholic Fatty Liver Disease

Statistical Analysis Plan

(SARO.17.010)

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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.17.010 study. This document is based on protocol version 7.0, dated 01 Aug 2019. 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 and interim or final analysis. Any changes from the planned analysis as described in the protocol are detailed here, and any differences described here supersede the analysis as 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

The objectives of this study are to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium in liver transplant recipients with nonalcoholic fatty liver disease (NAFLD) as assessed by Controlled Attenuation Parameter (CAP) and magnetic resonance imaging (MRI). Efficacy will be evaluated as a secondary objective.

Primary Objective

The primary objective of this study is to assess the safety of Saroglitazar magnesium 4 mg in liver transplant recipients with non-alcoholic fatty liver disease (NAFLD) over 24 weeks of treatment.

Secondary Objectives

The secondary objectives of this study are to assess:

- Changes in hepatic fat as determined by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE) from baseline to end of treatment (EOT)
- Changes in metabolic flexibility from baseline to EOT
- Changes in markers of insulin resistance [frequently sampled intravenous glucose tolerance test (FSIVGTT), glycosylated hemoglobin (HbA1c) and fructosamine] from baseline to EOT
- Changes in serum liver enzymes from baseline to EOT
- Changes in serum lipids from baseline to EOT
- Changes in atherogenic lipoprotein which including small dense low-density lipoprotein (sdLDL), LDL size and concentration, subtypes of very low-density lipoprotein (VLDL), high-density lipoprotein (HDL) from baseline to EOT
- Change in Quality-of-life score from baseline to EOT using SF-36 health survey
- Pharmacokinetics of Saroglitazar following first dose and last dose
- Body composition assessment via change in adipose tissue and skeletal muscle volume from baseline to EOT by whole body MRI.

2.2 Study Description

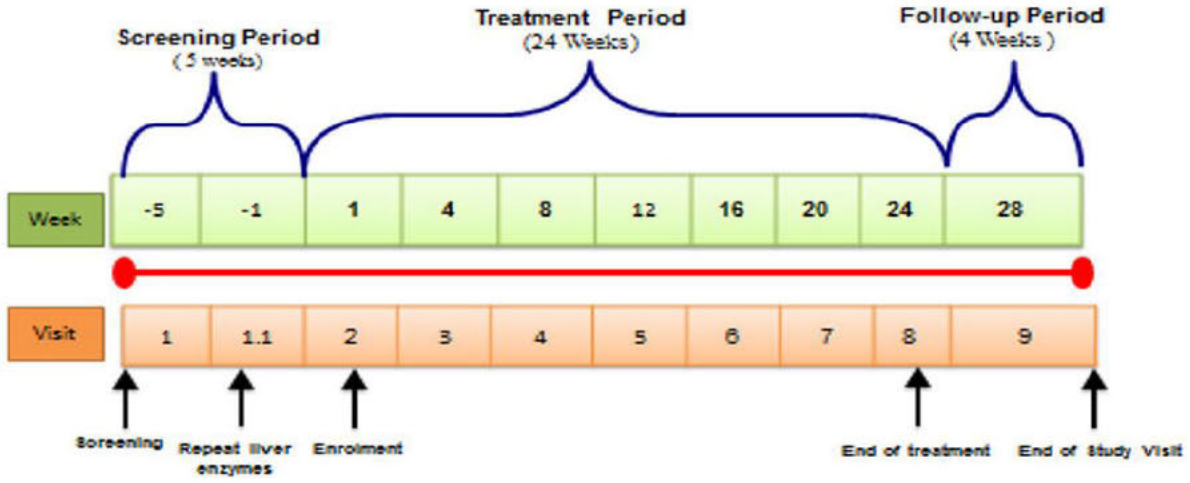
2.2.1 Study design

This is a Phase 2A prospective, single-center, open-label, single-arm study to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with non-alcoholic fatty liver disease. Patients who are at least 6 months post-transplant for non-alcoholic steatohepatitis (NASH) or cryptogenic cirrhosis thought to be secondary to NASH are eligible to be enrolled in this study. Approximately 15 male and female patients aged 18 to 75 years who meet the inclusion and exclusion criteria will be enrolled. All eligible patients will receive Saroglitazar magnesium 4 mg once daily in the morning for a period of 24 weeks.

This study will be conducted over a period of up to 33 weeks and will include a 5-week screening period, a 24-week treatment period and a safety follow-up visit, 4 weeks after the last treatment. The screening period may be extended under special circumstances with the explicit approval of the Sponsors' Medical Expert(s). The study visits will occur at Screening, Baseline (day 1), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 3 days), Week 12 (Day 85 ± 3 days), Week 16 (Day 113 ± 3 days), Week 20 (Day 141 ± 3 days) and Week 24 (Day 169 ± 3 days). A

safety follow-up visit will be conducted approximately 4 weeks after the administration of last dose of the study drug (Day 197 ± 3 days).

Approximately 5 patients will be included in the pharmacokinetic assessment. Pharmacokinetics of Saroglitazar will be assessed following administration of first (Baseline) and last dose (Week 24). The samples will be collected at Pre-dose (0.0) and 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 24 hours post-dose. In addition, pre-dose sample will be collected at Week 4, 8, 12, 16 and 20 Visits. The study plan is provided below.



2.2.2 Study plan

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2.3 Randomization

Not applicable. This is an open-label single-arm study and all eligible patients will receive Saroglitazar magnesium 4 mg treatment.

2.4 Blinding and Unblinding

The study is an open-label single-arm study. The study participants and the investigator will be aware about the study drug (Saroglitazar magnesium 4 mg), is to be administered.

2.5 Interim Analysis

No interim analysis is planned for this study.

3. ANALYSIS POPULATIONS

Patient 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 enrolled patients who receive at least one dose of study drug and have at least one post-baseline assessment visit. The mITT population will serve as the primary analysis 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 efficacy endpoints will be conducted using per-protocol (PP) population. The PP population includes all enrolled patients who receive at least one dose of study drug, complete the study (Week 24 assessment) in compliance with the protocol and do not have any major protocol violations.

The number of patients excluded from mITT and PP populations and a listing of excluded patients from each analysis population with reason for exclusion will be presented.

3.2 Safety Analysis Population

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

3.3 Pharmacokinetic Analysis Population

The pharmacokinetic population includes all enrolled patients with evaluable concentration profile and do not have any major protocol deviation(s) that could affect the PK profile of the study drug.

4. SAMPLE SIZE AND POWER CALCULATIONS

Due to exploratory nature of this study, no formal sample size estimation was performed. This study will enroll 15 patients and approximately 5 patients will be included in the pharmacokinetic assessment sub-study. The number of patients was chosen based on the clinical experience with other similar proof of concept studies.

5. PATIENT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Disposition of Patients

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

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, Body Mass Index (BMI), reproductive status, history of alcohol intake and liver biopsy performed will be summarized and tabulated for all 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 counts and percentage.

Medical history, previous and concomitant therapies

Medical history information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®, version 21.0). A summary will be provided including the frequency and percentage of patients with medical history terms by system organ class and preferred term for the safety population. A by-patient listing of medical history information will be provided for all enrolled patients 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 patients who had previous therapies/medications and a separate summary of patients 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 patients.

6. EFFICACY ANALYSIS STRATEGY

In this study, efficacy will be evaluated as a secondary objective.

6.1 General Considerations

Categorical variables will be summarized with the frequency and percentage of patients in each category. Continuous variables will be summarized descriptively with the number of patients, mean, standard deviation, minimum, median and maximum values. Change from baseline will be summarized similarly. 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® statistical software (version 9.4) application 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 patient 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 Endpoints

Efficacy Endpoints

The efficacy endpoints are:

- Changes in hepatic fat as determined by MRI-PDFF and MRE from baseline to Week 24 (EOT visit).
- Changes in metabolic flexibility from baseline to Week 24 (EOT visit).
- Changes in markers of insulin resistance (FSIVGTT, HbA1c and Fructosamine) from baseline to Week 24 (EOT visit).
- Changes in serum liver enzymes (ALT, AST, ALP and Total Bilirubin) from baseline to Week 24 (EOT visit).
- Changes in serum lipid profile (Total cholesterol, Triglycerides, HDL, LDL, VLDL and non-HDL) from baseline to Week 24 (EOT visit).
- Changes in atherogenic lipoprotein which includes sdLDL, LDL size and concentration, subtypes of VLDL and HDL from baseline to Week 24 (EOT visit).
- Change in QoL score from baseline to Week 24 (EOT visit) using SF-36 health survey
- Change in adipose tissue and skeletal muscle volume from baseline to Week 24 (EOT visit) assessed by whole body MRI.

Pharmacokinetic Endpoints

The PK parameters for Saroglitazar that may be calculated include the following:

- C_{max}: Peak plasma concentration
- T_{max}: Time to reach peak plasma concentration
- AUC_{0-t}: Area under the plasma concentration vs time curve from time 0 to last measurable concentration
- AUC_{0-inf}: Area under the plasma concentration vs time curve extrapolated to infinity
- AUC_{tau}: Area under the plasma concentration vs time curve in a 24 hour doing interval
- λ_z: Terminal elimination rate constant
- $t_{½}$: Terminal elimination half-life
- Vd/F: Apparent volume of distribution
- CL/F: Apparent clearance
- C_{min}: Minimal or trough plasma concentration for last dose only
- Accumulation index: Ratio of AUCtau (last dose)/AUCtau (first dose)
- Fluctuation index

6.3 Efficacy Hypotheses

There are no formal hypotheses testing will be conducted for the efficacy endpoints. The p-values presented for change from baseline are for the descriptive purpose only.

6.4 Statistical Methods for Efficacy Analyses

All efficacy endpoints will be summarized descriptively by visit. Descriptive summaries include number of patients, mean, standard deviation, median, minimum and maximum values will be provided for all efficacy endpoints. In addition, 95% confidence intervals will be provided for change from baseline to Week 24 (EOT visit) for all efficacy endpoints. Confidence intervals will be calculated using t-test. Quality of life assessment will be summarized using total scores as well as for each domain.

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 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. No testing of hypothesis will be conducted for this study.

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. Patients are required to have at least one post-baseline assessment 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.

7. ANALYSIS OF PHARMACOKINETIC ENDPOINTS

Pharmacokinetic analyses will be performed using the PK population.

Blood samples for pharmacokinetic analysis will be collected on Day 1 and Week 24 visit at Pre-dose (0.0), 0.5, 1.0, 2, 3, 4, 6, 8, 10 and 24 hour post-dose. In addition, pre-dose sample will be collected at Week 4, 8, 12, 16 and 20 visits.

The PK endpoints will be derived from the plasma concentration-time data for Saroglitazar for each patient, provided that there are sufficient data available to estimate each PK parameter. The AUC values will be calculated using the linear trapezoidal method. Actual sampling times of individual patient will be used in the PK analysis.

Descriptive summaries for plasma concentration (n, arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, and coefficient of variation) will be presented by sample collection time points. For calculating descriptive statistics for plasma concentrations, all post-dose plasma concentrations below the limit of quantification (BLQ) will be replaced by one half the lower limit of quantification (LLOQ). All pre-dose plasma concentrations below the limit of quantification (BLQ) will be replaced by zero. Plasma concentrations will be reported with three significant figures.

For the determination of PK parameters, actual collection times will be used as opposed to scheduled collection times.

Line plots (Linear and semi-log) of the mean concentration versus time curves will be plotted using scheduled times. Individual patient graphs will also be presented using actual times.

Descriptive statistics (number of patients, arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, and coefficient of variation) will be used to summarize the estimated pharmacokinetic parameters. All plasma-concentration data and PK parameter values will be provided in listings.

8. SAFETY ANALYSIS STRATEGY

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

8.1 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)
- 2D echocardiogram (ECHO)
- Physical Examination.

8.2 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 8.1.

8.3 Statistical Methods for Safety Analysis

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

8.3.1 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 tables 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 treatment compliance will also be presented using the following categories: < 80%, 80% to 120% and >120%. A patient is considered to be compliant, if he/she takes 80% to 120% of the study drug during the study period.

8.3.2 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.

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 21.0) dictionary. In addition to an overall presentation of all TEAEs, reports will be generated for special classes of TEAEs such as 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 patient will only be counted once.

Only patient listings will be provided for AEs that occur after signing informed consent but prior to exposure to study drug. These listings will comprise all events occurring during this period in any patient 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 drug and action taken.

8.3.3 Vital Signs

Vital signs parameters include blood pressure, pulse rate, oral temperature and respiratory rates. Vital signs assessments will be performed at screening, baseline and Week 4, 8, 12, 16, 20, 24 and 28 visits.

Descriptive summaries (N, mean, median, standard deviation, minimum and maximum values) of observed values and change from baseline in each vital sign parameter at each assessment visit will be presented. A listing will be provided for the vital sign parameter assessments for all enrolled patients.

8.3.4 Physical Examination

Physical examination assessments will be performed at screening, baseline and Week 4, 8, 12, 16, 20, 24 and 28 visits. Physical examination results will be listed for all enrolled patients.

8.3.5 Laboratory Results

Clinical laboratory evaluations consist of hematology, clinical biochemistry and urinalysis. Laboratory assessment for the urinalysis, lipid profiles and HbA1c will be performed at Screening, Baseline, Week 12 and Week 24 visits. Laboratory assessments for FSIVGTT and metabolic flexibility assessments will be conducted at Baseline and Week 24 Visits. Laboratory assessments for all other parameters will be performed at screening, baseline and Week 4, 8, 12, 16, 20, 24 and 28 visits. Laboratory values will be presented using the International System of Units (SI units).

Observed and changes from baseline values will be summarized descriptively (N, mean, median, standard deviation, minimum, and maximum values) for all hematology and biochemistry parameters at each assessment. 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, laboratory values that are listed as above or below particular thresholds will be numerically listed as above or below that threshold, respectively, by the minimum measured amount for that parameter. For example, if a parameter is measured to

A listing will be provided which contains data for each laboratory parameter for all enrolled patients.

8.3.6 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at Screening, Baseline, Week 12 and Week 24 visits. Descriptive summaries will be provided for all ECG parameters at each assessment visit. Descriptive summaries include number of patients, mean, standard deviation, minimum and maximum values. In addition, the overall interpretation of ECG results (normal, abnormal clinically insignificant, abnormal clinically significant) will be summarized as counts and percentages. A listing will be provided which contains data for each ECG parameter for all enrolled patients.

8.3.7 2D - Echocardiogram

A 2D echocardiogram (ECHO) will be performed at Baseline and Week 24 visit. The ECHO results (normal, abnormal clinically insignificant, abnormal clinically significant) will be summarized as counts and percentages. In addition, LV Ejection fraction will be summarized descriptively. A listing will be provided which contains data for each ECHO parameter for all enrolled patients.

9. REFERENCES

Not applicable

10. LIST OF ABBEVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BP	Blood pressure
BQL	Below the limit of quantification
CAP	Controlled attenuation parameter
ECG	Electrocardiogram
ECHO	Echocardiogram
EOT	End of treatment
FSIVGTT	Frequently sampled intravenous glucose tolerance test
HbA1c	Glycosylated hemoglobin
HDL	High density lipoprotein
ICH	International Council for Harmonisation
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PK	Pharmacokinetic
PP	Per-protocol
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sdLDL	Small dense low-density lipoprotein
SI	International System of Units
TEAE	Treatment Emergent Adverse Events
VLDL	Very low-density lipoprotein
WHO	World Health Organization