SAFETY DATA PLAN

NCT05211284

Protocol Number (Version no.)	SARO.20.001 (Version 4.0)
Study Title	A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial of Saroglitazar Magnesium for the Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in People Living with Human Immunodeficiency Virus (HIV) in the US.
Clinical Phase	2a
Sponsor's Signatory	[redacted]
Version Number	1.0
Site for Safety Evaluation	[redacted]
[redacted] **finalization**	29/11/2024

[redacted]

Table of Contents

List of Abbreviations:

AE	:	Adverse Event
ALT	:	Alanine Aminotransferase
AST	:	Aspartate transaminase
BP	:	Blood Pressure
CRF	:	Case Report Form
CSR	:	Clinical Study Report
eGFR	:	Estimated Glomerular Filtration Rate
ICH	:	International Council on Harmonization
IP	:	Investigational product
MedDRA	:	Medical Dictionary for Regulatory Activities
PI	:	Principal investigator
PLWH	:	People Living with Human Immunodeficiency Virus
PT	:	Preferred Term
R&D	:	Research and development
SAE	:	Serious Adverse Event
SAS	:	Statistical Analysis Software
SOC	:	System Organ Class
TEAE	:	Treatment Emergent Adverse Event
WHODD	:	WHO Drug Dictionary

Introduction:

The purpose of this document is to provide a description of the methods and procedures to be implemented for the presentation of safety data from Saroglitazar Magnesium 4 mg tablet, for trial SARO.20.001 version 4.0. This document is based on protocol dated 17th Nov 2023. Any revisions to this plan will be made prior to final analysis and reasons for such revisions will be described in the final Clinical Study Report. This study is terminated by sponsor's discretion and no primary efficacy endpoint data has been collected for any subject, hence no formal statistical analysis will be done for any efficacy endpoints. Hence, this safety data plan includes only data of screened and four subjects who were randomized in the study.

1 Objectives:

Safety Objectives:

1. To evaluate the safety and tolerability of Saroglitazar Magnesium 4 mg.

2 Study Design:

This phase 2a study is a randomized, placebo-controlled, double-blind, multicenter parallel-arm trial to evaluate the safety and efficacy of Saroglitazar Magnesium 4 mg compared with placebo in NAFLD in PLWH.

Number of Subjects:

In total, approximately 120 participants (60 participants in each treatment arm) were planned to receive either Saroglitazar 4 mg or placebo.

Randomization

Participants were randomized in a 1:1 ratio to receive Saroglitazar Magnesium 4 mg once daily orally or Placebo. The randomization scheme will be stratified by clinical center. Treatment assignments are double masked throughout the study until all data collection for the trial has been completed (i.e., after completion of the post-trial follow-up for all participants). The block randomization schedule was generated using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA).

Blinding and Un-blinding

The study is a double blind study with randomized subjects being treated with Saroglitazar Magnesium 4 mg, or Placebo. The essential aim of blinding is to prevent identification of the treatments by the investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

All members of the clinical study team, investigators and site staff will be blinded to treatment assignments while the study is in progress. In addition, Biostatistics staff who are directly involved in the analysis of the study results will remain blinded to treatment assignment while the study is in progress.

If necessary, the Sponsor may be required to unblind a subject if an adverse event (AE) meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfil expedited regulatory reporting requirements. In this event, the Sponsor Medical Expert will not divulge the treatment code to

any other personnel involved in reporting, obtaining, and/or reviewing the clinical evaluations. This level of blinding will be maintained throughout the conduct of the study.

In the event of a medical emergency during the study where the knowledge of subject treatment is required, an individual Principal Investigator will have the ability to unmask the treatment assignment for a specific subject. The Investigator should notify the Sponsor prior to unmasking a subject if there is sufficient time. Further, the Sponsor must be informed whenever the randomization code is broken. The reason for unblinding should be clearly and fully documented by the Investigator.

Once all study data have been verified, validated, and the database is locked, individual subjects will be unmasked to their treatment.
During this study, no unblinding done due to any safety reason.

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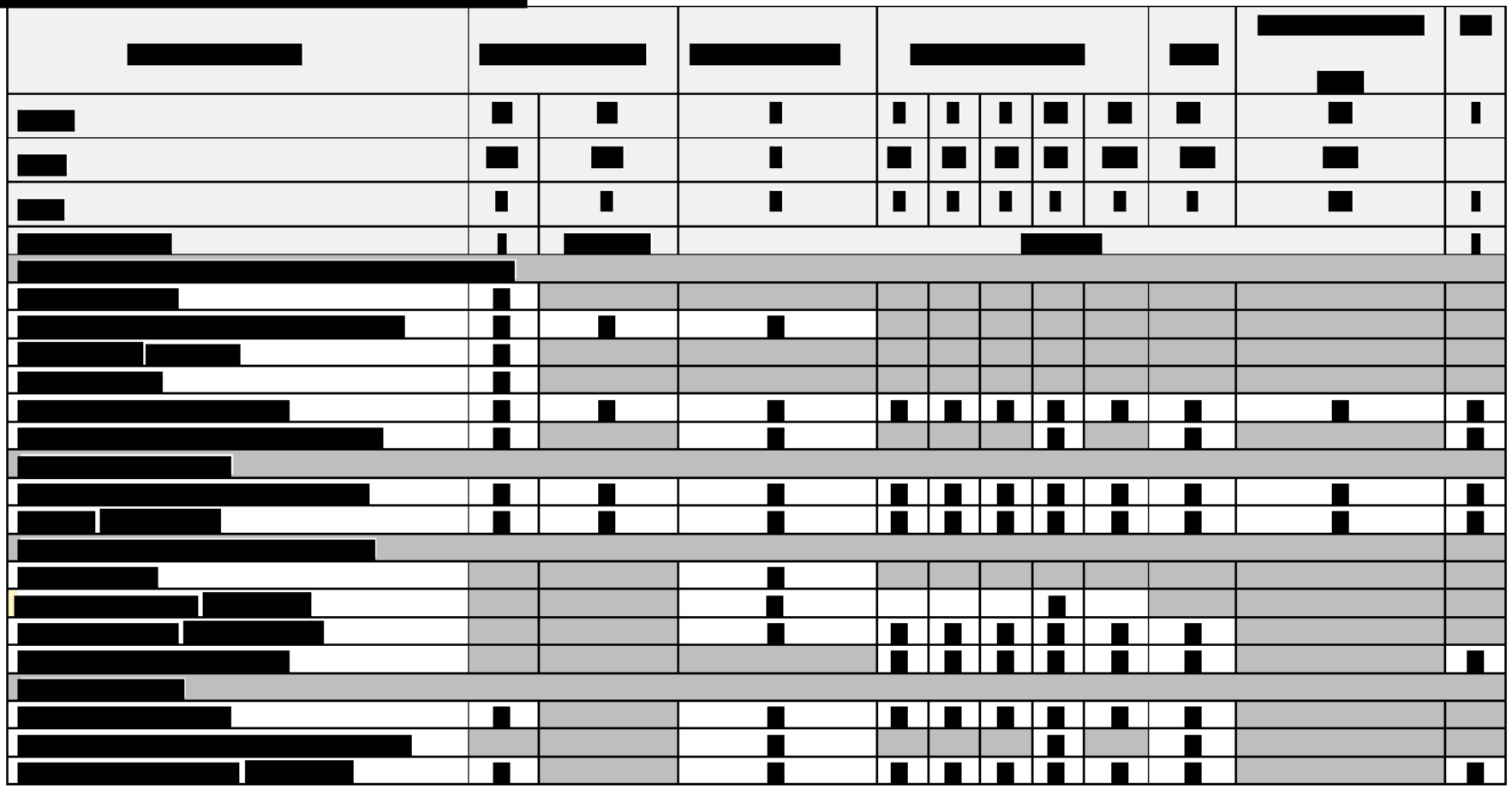
3 [redacted]

[redacted]



[redacted]

4 Protocol Deviations/ Violations/ Changes from Protocol:

Protocol deviation will be included in CSR.

For the purposes of this study, no distinction will be made between protocol violation and deviation. Deviation may be categorized as minor protocol deviation or major protocol deviation. Classification of protocol deviations as major or minor will be assessed at the blinded data review meeting prior to database lock. Minor protocol deviation includes any deviation that do not necessarily influence the results/outcome of primary endpoints or participant safety. Minor protocol deviation does not require immediate notification to the IRB unless otherwise specified by IRB requirements. All minor protocol deviations will be noted in monitoring reports and discuss with investigator/site personal. Major protocol deviation includes any violation, which may influence the results/outcome of primary endpoints or participant safety. Major protocol deviation must be reported immediately to the IRB, as specified by the IRB requirements. All major protocol deviations will be reported to the sponsor immediately (Note: persistent non-compliance of minor protocol deviations may rise to the level of major protocol deviations). As a result of protocol deviations, corrective actions are to be developed and implemented promptly.

The sponsor reserves the right to terminate the study at a given center in the event of monitoring and/or auditing findings of serious or persistent non-compliance with the protocol, Standard Operating Procedures (SOPs), GCP, and/or applicable regulatory requirement(s) by an investigator/Institution. In all cases of site closure due to protocol deviations, the IRB and regulatory authority will be informed. The clinical study report (CSR) will provide a list of protocol deviations/violations in a separate section. The results will be analyzed for all participants regardless of protocol deviation occurrence.

Protocol deviations/violations will include but are not limited to the following:

- Violations of inclusion and exclusion criteria at randomization.
- Participants who met the withdrawal criteria but were not withdrawn.
- Participants who received the wrong treatment or incorrect dose.
- Participants who received an excluded medication.
- Serious non-compliance with regulatory or GCP guidelines.

5 Concomitant Therapy:

All medications recorded during the study will be coded using the World Health Organization (WHO) Drug Dictionary (latest version). A summary will be provided for the frequency and percent of participants who had concomitant therapy/medications. Summaries will be provided by Anatomical Therapeutic Chemical (ATC) classification level 3 term and Preferred Name.

Refer the protocol section 8.8 Concomitant Medications in detailed for the previous and concomitant medications, Permitted, prohibited Concomitant Medications and other restrictions.

6 Analysis Populations:

All Enrolled Population: includes all participants who signed an ICF. This analysis population will be used to summarize participant disposition.

Safety Population: includes all participants who received at least one dose of study drug. Participants in the safety analysis population will be analysed according to the treatment received. This analysis population will be used for all safety analyses.

7 Demographic and Baseline Characteristics:

Demographic and baseline characteristics include age in years, gender, ethnicity, race, height (cm), weight (kg), body mass index (kg/m2), hip (cm) and waist circumference (cm).

Demographic and baseline characteristics will be summarized for safety 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 frequency and percentage.

8 Disposition of Subjects:

The number of subjects treated will be summarized.
The following summaries (number and/or percentage) will be included in the disposition table:
All enrolled subjects
Subjects in safety population
Subjects who completed the study
Subjects who discontinued from the study with reason for discontinuation

9 Medical History

The frequency count and percentage of patients experiencing any medical conditions will be tabulated by system organ classifications (SOC) and preferred term (PT) of MedDRA for all patients. The denominators for calculating the percentages will be based on number of patients in Safety Population. A data listing of medical history including medical and surgical history will be provided for Safety Population.

10 Data handling methodology:

Listing of subject data and tabulation of descriptive statistics be performed primarily using SAS® (version 9.4 or higher; SAS Institute Inc., USA).
The continuous variables will be summarized by n, mean, standard deviation, minimum, median and maximum. Categorical variables will be summarized with frequency and percentage.

10.1 Derived and Transformed Data:

Baseline:

In general, baseline will be defined as the last available, non-missing assessment prior to the administration of study assigned treatment.

10.2 Decimal Precision:

Unless otherwise noted, mean, median, standard deviation, minimum, maximum, percentage and any corresponding confidence interval will be presented to two decimal places.

10.3 Coding Dictionaries:

Adverse Events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA).

The actual dictionary versions used will be presented in the Clinical Study Report.

10.4 Values of Clinical Significance:

Reference ranges for all laboratory parameters collected throughout the study are provided by the respective laboratory. A laboratory value that is outside of the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range).

Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical significance.

The laboratory reference ranges will be provided on the listings of standardized laboratory data with out of range values flagged (low or high).

11 Handling of Drop-outs/ Premature Withdrawal:

All data compiled up to the point of discontinuation will be used for the data presentation. All withdrawals will be included in all analyses up to the time of withdrawal. Subjects who are withdrawn prematurely from study treatment will be included in all analyses regardless of the duration of treatment.

12 Statistical Methods and Analysis:

The data collected from CRF and laboratory test reports will be analyzed for demographics and safety. All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be presented by treatments and sorted by subject number and assessment date/time.

Demographic and baseline characteristics will be summarized by treatment. Subject disposition and reason for withdrawal will be listed and summarized. Unless otherwise stated, all the continuous variables will be represented by n, mean, standard deviation, minimum, median and maximum. All the categorical variables will be presented as frequency and percentage.

The change from baseline will be determined as:

Change = (last observed post dose value – pre dose).

13 Safety Analysis:

Subjects in safety population will be considered for the safety analysis.

13.1 Adverse Events:

Adverse Events will be coded using the MedDRA dictionary. Adverse Events will be grouped by SOC and PT and summarized by study treatment.

The summary tables will include the number of subjects and the number of events. For summaries by SOC and PT, a subject will be counted once at the SOC level and once at each PT within the SOC level.

- Relationships of definitely related, probably related, potentially related and Unknown will be judged as being treatment-related for the summary tables. Assessment of safety will be based on the frequency of TEAEs. All TEAEs seen during the study period will be listed. Separate listing will be provided for TEAE leading to discontinuation/other clinically significant non-fatal AE. Incidence of all TEAEs reported during the study in either of the group will be summarized by causality, severity and seriousness. Summaries for SAEs if any will also be provided.
  The following AE tables will be provided:
  - Overall Summary of Adverse Events by treatment
  - Summary of Treatment Emergent Adverse Events by system organ class and preferred term
  - Summary of Treatment Emergent Adverse Events by system organ class and preferred term by Severity.

13.2 Laboratory Evaluations:

Listings of individual subject laboratory results will be provided. Laboratory results and change from pre-dose values for lab tests will be summarized, at scheduled visits.

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 two decimal places, and has a result of "> 6" then, for summary purposes, the value of 6.01 will be used. Values with "<" or ">" will be classified as Low or High, respectively, unless such classifications aren't applicable for that parameter, in which case they will be classified as Normal.

13.3 Physical examinations:

All the physical examination will be listed by Subject no. by treatment.

13.4 Vital Signs:

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate and body temperature) will be listed at each protocol scheduled visit.

All the vital signs will be listed by Subject no. by treatment.

14 Revision History:

Version No.	Revision History	Reason for change
Not Applicable	Not Applicable	Not Applicable

15 Reference:

Protocol: SARO.20.001 (Version 4.0).

16 Appendix:

Appendix-01: Tables, Listings and Figures specifications