NCT05211284

Clinical Trial Protocol

Protocol No.:	SARO.20.001
Protocol Version Number and Date	Version 4.0, 17/NOV/2023
Reference IND No.	154765
Supersedes Protocol Version Number and Date	Version 3.0, 02/JUN/2022
Investigational: product(s)	Saroglitazar Magnesium
Scientific 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
Public Title:	**Saro**glitazar Magnesium 4 mg for **NA**FLD in **P**eople **L**iving with HIV in the **US** (SARONAPLUS)
Clinical Phase:	2a
Sponsor	**Zydus Therapeutics Inc.** 73C Route 31N, Pennington New Jersey 08534, USA
Sponsor's Signatory	**Deven V Parmar MD, FCP** [redacted]

Protocol Chair and Lead-Principal Investigator	[redacted]
Protocol Co-Chair	[redacted]
Medical Monitors	**Taufik Momin, MD** [redacted]
Clinical Laboratory	Each site will use its local laboratory
Data Management and Statistical Analysis:	[redacted]

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1. CLINICAL TRIAL PROTOCOL SUMMARY

Name of Sponsor:	**Zydus Therapeutics Inc.** 73C Route 31N, Pennington New Jersey 08534, USA
Name of Investigational product:	Saroglitazar Magnesium 4 mg
Name of active ingredient of investigational product	Saroglitazar Magnesium
Name of the comparator drug	Placebo
Name of active ingredient of comparator product	Placebo
Potential Indication	NAFLD with HIV
Study Participants	NAFLD with HIV
Number of Participants to be Randomized	Approximately 120
Number of site(s)	Approximately 8
Study Number:	SARO.20.001
Planned treatment Period	24 Weeks
Study Duration	36 Weeks
Title of study: 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	

Background:

Nonalcoholic fatty liver disease (NAFLD) is one of the most common types of chronic liver disease and the second leading cause for liver transplantation in the United States (US)[1, 2, 3].

The severity of NAFLD ranges from nonalcoholic fatty liver (simple steatosis) to nonalcoholic steatohepatitis (NASH)[4,5]. NASH is the most severe form of NAFLD and is characterized by hepatocellular injury, inflammation and risk of progression to NASH-related cirrhosis and NASH-related hepatocellular carcinoma. NAFLD is also considered to be the hepatic component of the metabolic syndrome, which includes dyslipidemia, peripheral insulin resistance, obesity, type 2 diabetes mellitus (T2DM), and hypertension[4,5].

NAFLD in people living with human immunodeficiency virus (PLWH) is not well studied. Numerous studies have been conducted to further understand the diagnosis, mechanisms, progression, and therapies of NASH[6-10]. However, all of these studies have systematically excluded PLWH, as NAFLD in these patients was thought to be different from that in the general population due to HIV itself, antiretroviral therapy (ART), concomitant medications, and co-infections. This resulted in major knowledge gap regarding NAFLD in the setting of HIV. Prevalence of NAFLD in PLWH in the US is not well defined. NAFLD is projected to become the leading cause of liver disease in the aging HIV population[11] The reported prevalence of NAFLD in mono-infected PLWH ranges from 15% to 54% when assessed by imaging modalities and the vibration-controlled transient elastography (VCTE), and up to 73% in studies

including liver biopsy, exceeding the reported prevalence of NAFLD in the general population [3, 12-18]. Obesity, insulin resistance and other components of the metabolic syndrome have been reported in some studies to increase the risk for NAFLD in PLWH [14,16, 19-22]

Currently, there are no available therapies for NASH in PLWH. There is tremendous interest in developing pharmacologic therapies for NASH in the general population, but these studies systematically exclude PLWH. There have been studies of tesamorelin[23] and aramchol[24] in PLWH with NAFLD with imaging endpoints, similarly this study of Saroglitazar Magnesium has been designed for NAFLD in PLWH with imaging endpoints.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary objective	Primary endpoint
To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in hepatic fat content measured by MRI Proton Density Fat Fraction (MRI PDFF).	Change from baseline in hepatic fat content at week 24/EOT.
Secondary objectives	**Secondary endpoints**
1) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on improvement of hepatic fat content as measured by MRI PDFF.	1) Proportion of participants with reduction of at least 30% in hepatic fat content from baseline to Week 24/EOT
2) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in FibroScan®/Vibration-controlled transient elastography [VCTE]	2a) Change from baseline in LSM at Week 24/EOT. 2b) Change from baseline in continuous CAP at Week 24/EOT. 2c) Change from baseline in FAST score at Week 24/EOT
3) To evaluate the effects of Saroglitazar Magnesium 4 mg compared with Placebo on changes in non-invasive markers of fibrosis and steatosis.	3a) Change from baseline in plasma pro-collagen type 3 (PRO-C3) levels at Week 24/EOT. 3b) Change from baseline in Fibrosis-4 (FIB-4), AST to Platelet Ratio Index (APRI), and NAFLD Fibrosis Score (NFS) at Week 24/EOT.
4) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on liver enzyme, lipid profile, and fasting glucose	4a) Change from baseline in liver enzyme parameters (ALT and AST) at Week 24/EOT. 4b) Change from baseline in triglyceride [TG) high-density lipoprotein [HDL], low-density lipoprotein [LDL], very low-density

	lipoprotein [VLDL], total cholesterol, and non-HDL cholesterol, at Week 24/EOT. 4c) Change from baseline in fasting plasma glucose (FPG) at Week 24/EOT.
5) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on anthropometric measurements.	5) Change from baseline in body weight, BMI, hip circumference, and minimum waist circumference at Week 24/EOT
6) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in health-related quality of life scores measured by SF-36 Questionnaire.	6) Change from baseline in SF-36 Questionnaire mental (MCS) and physical components scores (PCS) at Week 24/EOT.
Safety objectives	**Safety Assessments**
1. To evaluate the safety and tolerability of Saroglitazar Magnesium 4 mg compared with placebo.	1a) Frequency and severity of Treatment-Emergent Adverse Events (TEAE), Serious Adverse Events (SAEs), and Adverse Events of Special Interest (AESI) 1b) Changes in clinical laboratory testing parameters (hematology, clinical chemistry, and urinalysis) 1c) Changes in vital signs (blood pressure, pulse rate, temperature and respiratory rate) 1d) Changes in physical examination assessments

Criteria for Inclusion/Exclusion:

Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Adults (≥18 years of age) with documented HIV.
2. Documented diagnosis of NAFLD established by imaging (ultrasound, CT scan or MRI) or liver biopsy within 6 months before screening, based on American Association for the Study of Liver Disease [AASLD] criteria.
3. Hepatic fat fraction ≥8% by MRI-PDFF.
4. ALT level ≥31 U/L in men and ≥19 U/L in women at visit 1 and 2.
5. HIV-1 RNA <200 copies/mL for ≥6 months on ART (must have screening HIV-1 RNA value and one clinical care value within 6 months prior to screening and up to the randomization that meets the criteria).
6. Stable ART regimen for ≥3 months prior to screening and stable up to the randomization and no active plans to change ART while on study.
7. Willingness to participate in the study .

Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. History of significant alcohol consumption (defined as >2 drinks/day on average for men, >1 drinks/day on average for women) for at least 3 consecutive months (12 consecutive weeks) within 5 year before screening (Note 1: 1 drink =12 ounces of beer, 8-9 ounces of malt liquor, 4 ounces of wine or 1 ounce of spirits/hard liquor. Note 2: Use sex assigned at birth for alcohol consumption limits).
2. History of other acute or chronic liver disease, including, but not limited to autoimmune, primary biliary cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis, hepatitis B virus (HBV), and ongoing or recent (within the past 3 years) hepatitis C RNA positivity. (Exceptions: a. Participants with previously treated hepatitis C infection are eligible for consideration if their sustained virologic response was achieved more than 3 years prior to screening. The proportion of such participants in this trial will not exceed 25% of the study cohort. b. Participants with prior acute HBV infection that is resolved but currently do not have hepatitis B surface antigen (HBsAg) or detectable HBV Deoxyribonucleic acid (HBV DNA) are eligible).
3. History of liver transplant.
4. Liver biopsy or radiologic imaging consistent with the clinical presence of cirrhosis or portal hypertension at screening.
5. Participants whose Visit 2 ALT, AST, or alkaline phosphatase (ALP) values exceed their Visit 1 values by more than 50%.

   Note: These participants will be required to have a third value measured at-least one week after V2, to assess for a trend. If the third value shows a continued increase ≥10% compared to the Visit 2 values, the participant is considered ineligible for randomization.

6. Ongoing use of steatogenic medications or supra-physiologic hormonal therapies (exception: transgender women on stable dose [for ≥3 months] of feminizing hormonal therapy), within 3 months prior to screening until time of randomization or anticipated use of medications that cause significant changes in weight during the study period; (Refer Appendix 7 for 'List of Steatogenic Medications Or Supra-Physiologic Hormonal Therapies Or Medications That Cause Significant Weight Change').
7. Uncontrolled type 2 diabetes mellitus, defined as HbA1c >9.5% at screening.
8. Any of the following laboratory values at screening:

   a. ALT or AST >250 U/L.

b. Total bilirubin >1.5 mg/dL and direct bilirubin > 0.5 mg/dL (unless due to Gilbert's disease or atazanavir use per the opinion of the site investigator).
c. Platelet count <150,000/mm^3.
d. Estimated glomerular filtration rate (e-GFR) <60 mL/min/1.73m^2 using the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation (Refer Appendix 6 for 'CKD-EPI Calculator').
e. International normalized ratio (INR) >1.3.
f. Albumin < 3.6 g/dL

9. History of malignancy in the past 5 years and/or active neoplasm with the exception of superficial, non-melanoma, skin cancer.
10. Unstable cardiovascular disease, including:

    a. Unstable angina, (i.e., new or worsening symptoms of coronary heart disease) and/or acute myocardial infarction within the 3 months preceding screening
    b. Acute coronary syndrome or coronary artery intervention, within the 3 months preceding screening
    c. Heart failure of New York Heart Association (NYHA) class (III-IV) or worsening congestive heart failure within the 6 months preceding screening.
    d. History of (within 3 months preceding screening) or current unstable cardiac dysrhythmias.
    e. Uncontrolled hypertension (systolic blood pressure [SBP] >155 mm Hg and/or diastolic blood pressure [DBP] >95 mm Hg) at screening.
    f. Stroke or transient ischemic attack within the 6 months preceding screening.

11. Unstable pulmonary disease (based upon site investigator's evaluation) at screening.
12. Use of drugs that are known CYP2C8 inhibitors/substrates (Refer Appendix 2 for the 'List of Known CYP2C8 inhibitors/substrates') in the last 28 days preceding screening.
13. History of severe illness or any other conditions (such as poorly controlled psychiatric disease, active gastrointestinal conditions that might interfere with drug absorption, etc.) that require systemic treatment/or hospitalization, until participant either completes therapy or is clinically stable on therapy as per the opinion of the site investigator, for at least 7 days prior to screening.
14. Use of thiazolidinediones or Telmisartan within 3 months prior to screening until time of randomization.
15. Use of unstable doses of sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g. canagliflozin, empagliflozin, dapagliflozin, etc.), glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon-like peptide (GLP)-1 agonists (e.g. semaglutide, exenatide, liraglutide, lixisenatide, tirzepatide etc.) within 6 months prior to screening until time of randomization.

16. Use of pentoxifylline, ursodeoxycholic acid, antioxidants such as vitamin E (>200 IU/day), glutathione, orlistat, betaine, or non-prescribed complementary alternative medications within 6 months prior to screening until time of randomization.
17. Known allergy, sensitivity or intolerance to the study medication or formulation ingredients.
18. History of any known bleeding disorder or coagulopathy.
19. Any condition that in the opinion of the site investigator, would compromise the participant's ability to participate in the study.
20. Unstable doses of anti-diabetic agents, including sulfonylureas, biguanides or dipeptidyl peptidase-4 (DPP-4) inhibitors in the 3 months prior to screening until time of randomization.
21. Unstable doses of lipid-lowering agents such as statins (e.g. simvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin, etc.) or fibrates (clofibrate, Fenofibrate) in the 3 months prior to screening until time of randomization.
22. Participant with weight change >5% within 6 months prior to screening until time of randomization.
23. History of bariatric surgery or currently undergoing evaluation for bariatric surgery.
24. Participation in another interventional clinical study and/or receipt of any other investigational medication within 3 months prior to screening
25. History of COVID-19 infection in the last 30 days prior to screening.
26. Pregnancy-related exclusions, include:

    a. Pregnant/lactating female (including positive pregnancy test at screening)
    b. Pregnancy should be avoided by male and female participants either by complete abstinence or the use of acceptable effective contraceptive measures for the duration of the study and for at least 1 month after the end of the study treatment. Refer Appendix 3 Contraceptive Guidance

27. Participants having an absolute contraindication to MRI (eg., any implants, magnetic metals, cardiac pacemakers, neurostimulator) as per investigators' discretion

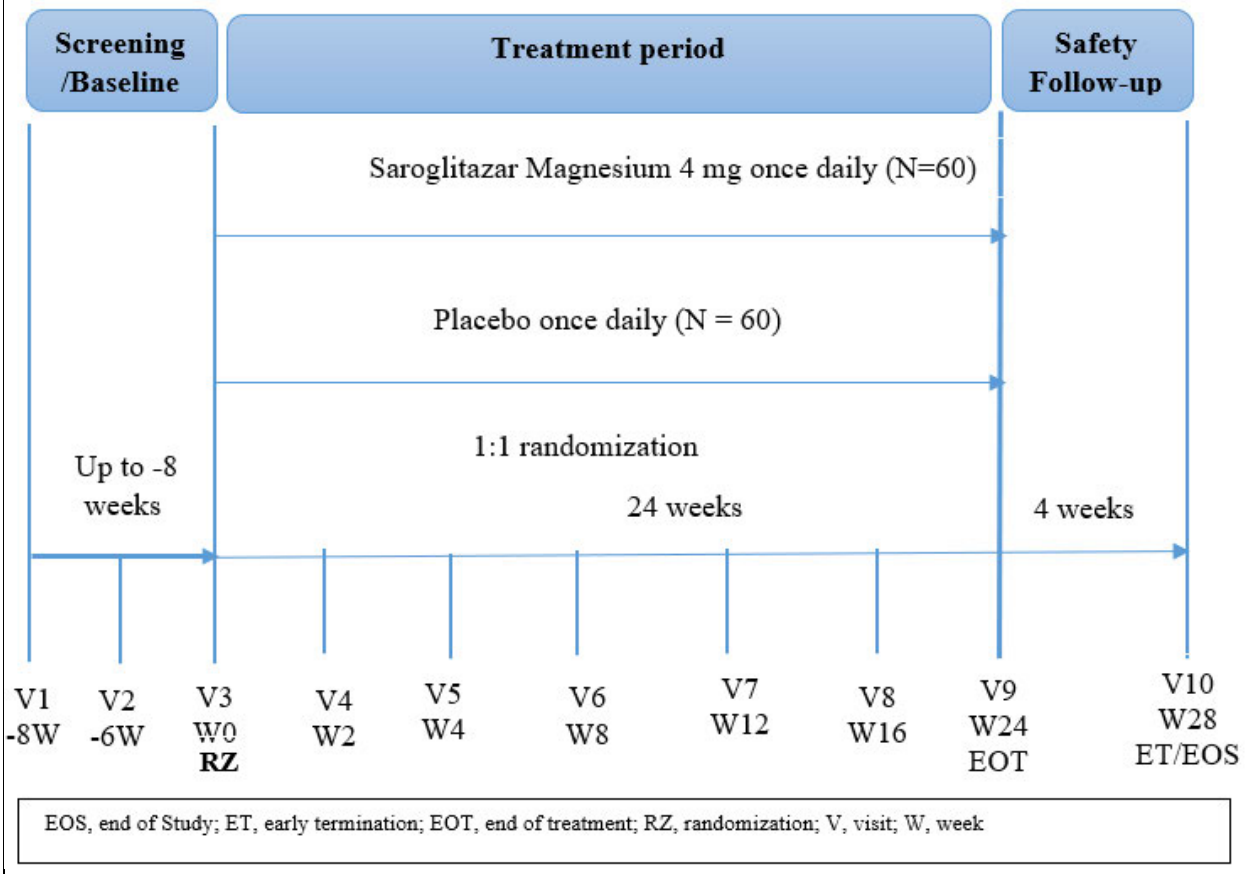
Trial Design: This phase 2a study is a randomized, placebo-controlled, double-blind, multicenter parallel-arm trial to evaluate the safety and efficacy of Saroglitazar Magnesium 4 mg compared with placebo in NAFLD in PLWH. Eligible participants will be randomized in a 1:1 ratio to receive Saroglitazar Magnesium 4 mg or placebo. This study plans to enroll approximately 120 PLWH with NAFLD from within the catchment area of approximately 8 participating clinical centers or community HIV practices in the US. The study will be conducted over a period of 36 weeks, including upto 8-week screening period, 24-week treatment period, and 4-weeks safety follow-up period (Figure 1 and Section 2 Schedule of Assessments). Participants will be evaluated at the study sites for 10 scheduled visits.

- Screening: Week -8 (Visit 1) and Week -6 (Visit 2); Screening period will last up to 8 weeks. Visit 2 must occur at least 14 days after Visit 1.

- Randomization: Day 1 (Visit 3) can occur at any time point after visit 2 but within 8 weeks of screening period and participant can be randomized upon confirmation of eligibility criteria.
- Treatment Period: Week 0 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (Visit 8), Week 24/EOT (Visit 9).
- Safety Follow-up: Week 28 (Visit 10)

Participants will be monitored during the study at every visit for the development of any AEs, including treatment-emergent AEs and AEs of special interest (weight gain and DILI).

The study scheme is provided in Figure 1.



EOS, end of Study; ET, early termination; EOT, end of treatment; RZ, randomization; V, visit; W, week

Total Enrollment:	Approximately 120 participants (60 in each of the Saroglitazar Magnesium 4 mg and Placebo arms)
Test product: **Mode of administration:**	Saroglitazar Magnesium 4 mg tablets Oral (once daily in the morning before breakfast without food)
Reference therapy: **Mode of administration:**	Placebo tablets Oral (once daily in the morning before breakfast without food)
Duration of treatment:	24 weeks

Statistical Methods:

Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock. The SAP will include detailed statistical aspects of the efficacy and safety analysis. Statistical analysis will be performed using SAS software (version 9.4 or higher) (SAS Institute Inc., USA). Demographic characteristics and baseline characteristics will be summarized by treatment, subject disposition, reasons for withdrawal, or by any other variables, as appropriate. 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 counts and percentages.

The primary efficacy endpoint is the change from baseline in hepatic fat content at Week 24/EOT as measured by MRI-PDFF.

Comparison of change from baseline in hepatic fat content between Saroglitazar 4 mg and placebo will be evaluated using mixed models for repeated measures (MMRM) including visit and treatment as factors, baseline value as a covariate and an interaction term treatment x visit. The p-value for the treatment differences (Saroglitazar Magnesium versus Placebo), estimate of LSMEANS treatment difference (Saroglitazar Magnesium – Placebo), and the two-sided 90% confidence interval of the LSMEANS difference will be generated from the MMRM model. Observed values and changes from baseline will be summarized descriptively at each visit for all continuous parameters.

All continuous secondary and exploratory efficacy endpoints will be analyzed similar to the primary efficacy endpoints and the categorical variables will be analyzed using the chi-square test. All statistical analysis will be conducted at one-sided alpha of 0.05.

All safety parameters will be summarized descriptively.

Sample Size Justification:

The primary efficacy endpoint is the mean change from baseline in hepatic fat content assessed by MRI-PDFF at Week 24/EOT in PLWH with NAFLD. In a previously conducted Phase 2 study in NAFLD participants, the mean change from baseline in hepatic fat content at Week 16 in Saroglitazar 4 mg group was -4.2 (SD=6.2) and in Placebo was -0.3 (SD=5.7)[30].

Assuming a similar treatment effect on hepatic fat content in Saroglitazar 4 mg group at Week 24/EOT in this study, a sample size of 102 participants (51 participants in each treatment arm) will provide 80% power to detect a treatment difference of at least 3 in change from baseline in hepatic fat content at Week 24 between Saroglitazar 4 mg and Placebo using a one-sided 5% level of significance based on two-sided t-test, assuming a common standard deviation of 6.

Assuming a dropout rate of 15% at week 24, approximately 120 participants (60 participants in each treatment arm) will be randomized in a 1:1 ratio to receive either Saroglitazar 4 mg or placebo.

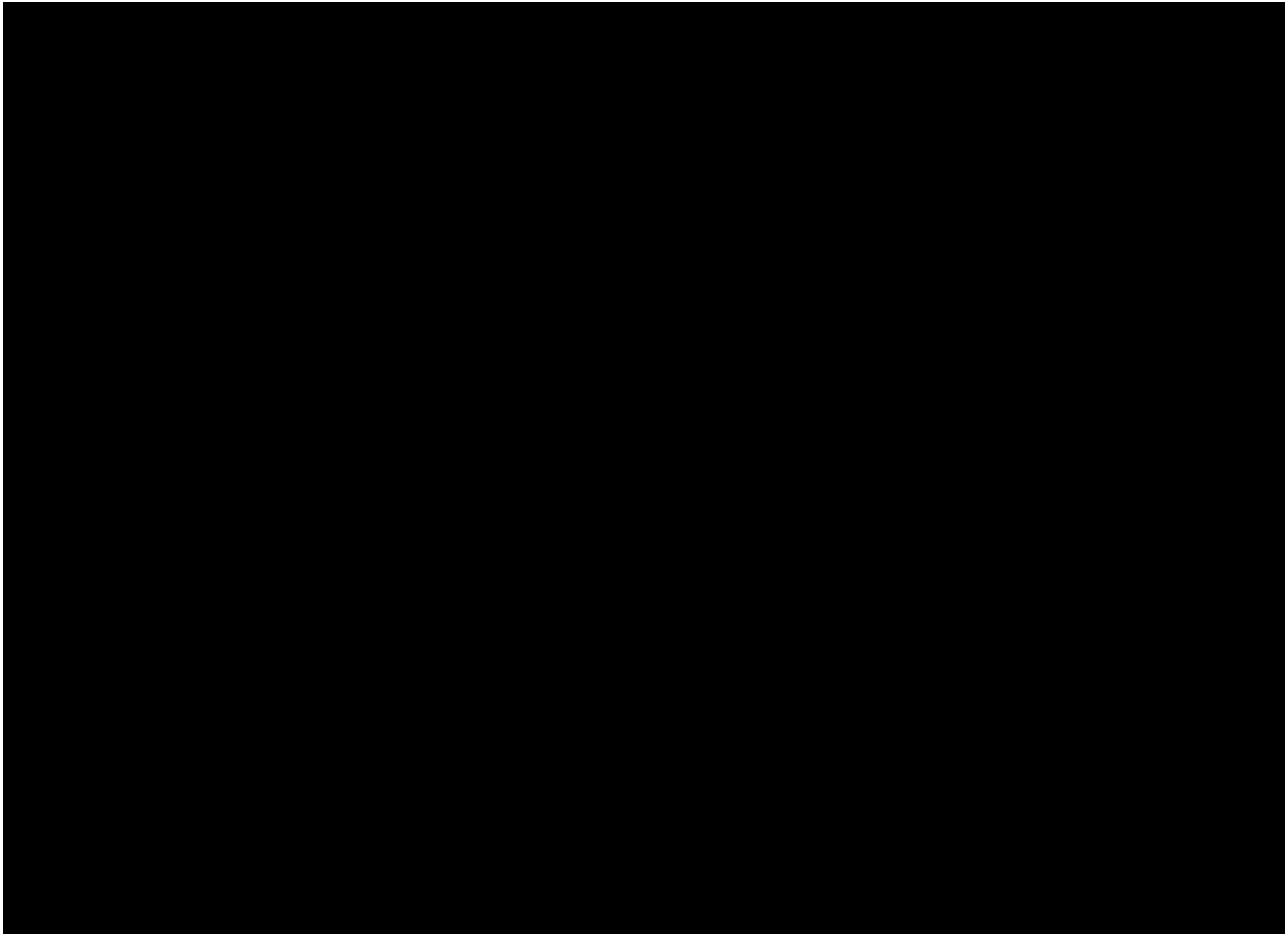
Data and Safety Monitoring Board:

For the trial, an external oversight will be provided by an unblinded Data and Safety Monitoring Board (DSMB). Further information on the DSMB review process will be provided in a separate charter of DSMB.

Hepatic Safety Adjudication Committee:

A separate blinded Hepatic Safety Adjudication Committee (HSAC) will be established. The committee will review, monitor and adjudicate possible cases of Drug Induced Liver Injury (DILI) in the study.

2. SCHEDULE OF ASSESSMENTS



3. ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
APRI	Aspartate aminotransferase to Platelet Ratio Index
Apo	Apolipoprotein
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUDIT	The Alcohol Use Disorders Identification Test
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CAP	Controlled attenuation parameter
CBC	Complete blood count
CFRs	Code of federal regulations
CKD-EPI	Chronic kidney disease-epidemiology collaboration
CMH	Cochran-Mantel-Haenszel
CMP	Comprehensive metabolic panel
cGMP	Current-Good Manufacturing Practices
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CYP	Cytochrome P-450
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4
DSMB	Data and Safety Monitoring Board
EC_{50}	Half maximal effective concentration
EDC	Electronic data capture
e-GFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis
EOT	End of Treatment
EOS	End of Study
ET	Early Termination
FAST	Fibroscan-AST
FDA	Food and Drug Administration
FIB-4	Fibrosis-4 index

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GIP	glucose-dependent insulinotropic polypeptide
GLP 1 RA	Glucagon-like peptide receptor agonist
HAV IgM	Hepatitis A virus immunoglobulin M
HbA1c	Glycosylated hemoglobin
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HSAC	Hepatic Safety Adjudication Committee
HR	Heart rate
HR-QOL	Health-related quality of life
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)
ITT	Intent-to-treat
INR	International normalized ratio
IP	Investigational product
IRB	Institutional review board
IWRS	Interactive Web Response System
LDL	Low-density lipoprotein
LFT	Liver Function test
LoE	Lack of Efficacy
LPL	Lipoprotein lipase
LSM	Liver stiffness measurement
LSMEANS	Least Squares Means
MTD	Maximum tolerated dose
MAR	Missing at random
MI	Multiple Imputation
MNAR	Missing not at random
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
NFS	NAFLD Fibrosis Score
NYHA	New York Heart Association
ox-LDL	Oxidized LDL
PRO-C3	Procollagen 3
PPARs	Peroxisome proliferator-activated receptors
PLWH	People living with human immunodeficiency virus

RIR	Relative improvement ratio
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Short Form-36
SGLT2	Sodium-glucose cotransporter-2 inhibitors
sIRB	Single IRB
SOPs	Standard operating procedures
SUSARs	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse events
TG	Triglyceride
ULN	Upper limit of normal
US	United States
VCTE	Vibration-controlled transient elastography
VLDL	Very low-density lipoprotein
WBC	White blood cell

4. TABLE OF CONTENTS

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5. INTRODUCTION

5.1 BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is one of the most common types of chronic liver disease and the second leading cause for liver transplantation in the United State (US)[1, 2, 3]. The severity of NAFLD ranges from nonalcoholic fatty liver (simple steatosis) to nonalcoholic steatohepatitis (NASH)[4,5]. NASH is the most severe form of NAFLD and is characterized by hepatocellular injury, inflammation and risk of progression to NASH-related cirrhosis and NASH related hepatocellular carcinoma. NAFLD is also considered to be the hepatic component of the metabolic syndrome, which includes dyslipidemia, peripheral insulin resistance, obesity, type 2 diabetes mellitus (T2DM), and hypertension[4,5].

NAFLD in people living with human immunodeficiency virus (PLWH) is not well studied. Numerous studies have been conducted to further understand the diagnosis, mechanisms, progression and therapies of NASH[6-10]. However, all studies have systematically excluded PLWH, as NAFLD in these patients was thought to be different from that in the general population due to HIV itself, antiretroviral therapy (ART), concomitant medications, and co-infections. This resulted in major knowledge gap regarding NAFLD in the setting of HIV. Prevalence of NAFLD in PLWH in the US is not well defined. NAFLD is projected to become the leading cause of liver disease in the aging HIV population[11]. The reported prevalence of NAFLD in mono-infected PLWH ranges from 15% to 54% when assessed by imaging modalities and the vibration-controlled transient elastography (VCTE), and up to 73% in studies including liver biopsy, exceeding the reported prevalence of NAFLD in the general population [3, 12-18]. Obesity, insulin resistance, and other components of the metabolic syndrome have been reported in some studies to increase the risk for NAFLD in PLWH[14, 16, 19-22].

Currently, there are no available therapies for NASH in PLWH. There is tremendous interest in developing pharmacologic therapies for NASH in the general population, but these studies systematically exclude PLWH. There have been studies of tesamorelin[23] and aramchol[24] in PLWH with NAFLD with imaging endpoints, similarly this study of Saroglitazar Magnesium has been designed for NAFLD in PLWH with imaging endpoints.

5.2 RATIONALE FOR CONDUCTING THE STUDY

There is a strong scientific rationale for targeting the peroxisome proliferator-activated receptors (PPAR) axis to improve metabolic dysfunction and hepatic steatosis in PLWH. Saroglitazar Magnesium is a novel PPARα/γ agonist having predominant PPARα and moderate PPARγ actions[5]. Saroglitazar Magnesium is currently approved for treating “diabetic dyslipidemia and hypertriglyceridemia in T2DM not controlled by statin” (February 2013), “add-on therapy to metformin for treatment of type 2 diabetes mellitus” (January 2020), “non-cirrhotic nonalcoholic steatohepatitis” (March 2020), ‘NAFLD with comorbidities (Either Obesity, T2DM, Dyslipidemia or Metabolic Syndrome)’ (since December 2020) in India, and has a well-estabilshed safety profile.

Saroglitazar Magnesium has shown improving steatohepatitis in a number of established animal models, improving hepatic steatosis, inflammation, and ballooning, and preventing the development of fibrosis more prominently than pioglitazone and fenofibrate. In a diet-induced-obesity NASH model, Saroglitazar Magnesium was associated with 18% weight loss; reduced serum levels of alanine aminotransferase (ALT), total cholesterol, and triglycerides (TG); and significantly reduced steatosis and necroinflammation[26].

In a pooled analysis from several phase 2 trials of dyslipidemia in both diabetic and non-diabetic adults (who have high prevalence of NAFLD), Saroglitazar Magnesium administered for 12 weeks was associated with improvement in serum ALT, lipids, and glucose control in a dose-dependent manner. Commonly reported adverse events (AEs) include nausea, pyrexia, headache, gastritis, and constipation. Serious AEs (SAEs) observed with other PPARγ agonists, such as weight gain, heart failure, cardiac events, bone loss, or DILI, have not been reported[27].

In a 12-week, open label study to treat lipodystrophy-related hypertriglyceridemia in PLWH on stable ART, Saroglitazar Magnesium 4 mg daily showed significant improvement in TG, very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), ALT, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP). The frequency of AEs was 8%, and all but one event (severe abdominal pain that resolved) were mild to moderate in nature[28]. *In vitro*, Saroglitazar Magnesium does not significantly inhibit or induce human cytochrome P-450 (CYP) isoenzymes, including CYP3A4.

For this trial, the 4 mg daily oral dose was chosen based on pharmacokinetics, dose ranging studies, the previous HIV lipodystrophy study, as well as two studies in primary NAFLD.

Therefore, this randomized, double-blind, placebo-controlled study is designed to evaluate the efficacy and safety of Saroglitazar Magnesium 4 mg for treatment of NAFLD in PLWH.

5.3 DRUG PROFILE

[redacted]

Saroglitazar Magnesium, through PPARα agonist action, increases the hepatic oxidation of fatty acids and lowers the synthesis and secretion of TG, which leads to increased diversion of fatty acids from tissues in the periphery to the liver. Saroglitazar Magnesium also increases lipolysis, removes TG-rich particles from plasma by activating lipoprotein lipase (LPL), and reduces production of apolipoprotein (Apo) C-III, which is an inhibitor of LPL activities. Saroglitazar Magnesium also reduces LDL and increases HDL, Apo A-I, and Apo A-II. Saroglitazar

Magnesium, through PPARγ agonist action, regulates the transcription of insulin-responsive genes and thereby increases insulin sensitivity, increases glucose uptake, and reduces blood glucose level [29].

The drug was developed with an expectation to achieve optimum anti-dyslipidemic and anti-hyperglycemic effects, while avoiding AEs such as peripheral edema, weight gain, cardiovascular events, renal and/or liver toxicity etc., which are commonly seen with other dual PPAR or PPARγ agonists. The pharmacological effects of Saroglitazar Magnesium were extensively evaluated in various pre-clinical models and clinical trials [29, 30, 32, 33].

Preclinical Experience

Extensive pre-clinical trials were done with Saroglitazar Magnesium using various animal models wherein, half maximal effective concentration (EC_{50}) of PPARα: PPARγ > 300; In vitro Saroglitazar Magnesium resulted in a 4615-fold higher activation of human PPARα (EC_{50} = 0.650 pM) than activation of human PPARγ (EC_{50} = 3 nM) in a transactivation assay. Saroglitazar Magnesium favorably modulated the lipid and glucose profile[32, 33]. Non-clinical pharmacological studies showed no significant safety concern at any of the doses tested.

In experimental NASH model (animal model of mice with choline-deficient, high-fat diet-induced NASH), Saroglitazar Magnesium reduced hepatic steatosis, ballooning, and inflammation; prevented development of fibrosis; and also reduced ALT, aspartate aminotransferase (AST), and expression of inflammatory and fibrosis biomarkers[26]. In this experimental NASH model, Saroglitazar Magnesium (3 mg/kg) significantly reduced the overall NAFLD activity score (NAS) compared to pioglitazone (25 mg/kg) and fenofibrate (100 mg/kg)[26]. In carbon tetrachloride-induced fibrosis model, Saroglitazar Magnesium (4 mg/kg) exhibited anti-fibrotic effect [26].

Clinical Experience

Maximum tolerated dose (MTD) in Phase 1 study was 16 mg/day for 10 days. In a Phase 1 study of a total of 136 healthy human volunteers, Saroglitazar Magnesium was found to be well tolerated in single as well as multiple doses without any safety concern. Several Phase 2 studies were conducted to evaluate the safety and efficacy of Saroglitazar Magnesium in dyslipidemic participants with and without diabetes, participants with impaired glucose tolerance test, and participants with NASH[29].

NAFLD/NASH Clinical Development:

The clinical evidence of the efficacy of Saroglitazar Magnesium in NASH has been evaluated in two Phase 2 studies in the US, one Phase 2 study in India, and one Phase 3 study in India, and one phase 3 study in Mexico. ALT level, which is a clinically accepted endpoint for the NASH trials

was used as the endpoint in two Phase 2 studies. The NAS, which is evaluated through liver biopsy was the endpoint in one Phase 2 study and two Phase 3 studies.

A Phase 2 study of 12 weeks duration was conducted to evaluate the safety and efficacy of Saroglitazar Magnesium 4 mg in 32 patients with biopsy-proven NASH along with ALT >1.5 times the upper limit of normal (ULN) (CTRI identifier: CTRI/2010/091/000108). There was a statistically significant reduction in the ALT levels (U/L) from baseline (95.86 ± 37.65) to Week 6 (52.79 ± 28.42) and Week 12 (44.37 ± 35.43). There was also a statistically significant decrease in HOMA-IR from baseline to Week 12. In patients with baseline TG ≥150 mg/dL, there was also a statistically significant reduction in TG (mg/dL) from baseline (247.15 ± 63.24) to Week 12 (185.31 ± 72.01).

In the US, a Phase 2 study of 16 weeks duration was conducted to evaluate the efficacy and safety of Saroglitazar Magnesium 1 mg, 2 mg, and 4 mg compared to placebo in 106 adult subjects with NAFLD/NASH along with ALT ≥50 U/L[30]. Percentage change in ALT levels from baseline to Week 16 was the primary efficacy endpoint. The change in mean ALT from baseline to Week 16 was -26.2±33.4% with Saroglitazar Magnesium 1 mg, -27.0±26.5% with Saroglitazar Magnesium 2 mg, and -44.9±26.2% with Saroglitazar Magnesium 4 mg compared to 2.6±32.1% with placebo ($p<0.001$ for all). Saroglitazar Magnesium 4 mg, compared to placebo, significantly reduced mean liver fat content (LFC) measured by magnetic resonance-proton density fat fraction [-4.21±6.23% versus -0.28±5.41%, p=0.002] at week 16. Saroglitazar Magnesium 4 mg was associated with improvements in enhanced liver fibrosis score, glycemic parameters, and atherogenic dyslipidemia at week 16. Lipoprotein analysis of serum samples obtained at baseline and week 16 from subjects was done using the Liposcale® test, a previously reported two-dimensional proton nuclear magnetic resonance spectroscopy (2D-1H-NMR) (OWL Metabolomics, Derio, Spain). Saroglitazar Magnesium improved CVD risk in subjects with abnormal baseline lipoprotein levels. Saroglitazar Magnesium reduced LDL-TG, VLDL-TG the ratio HDL-TG/HDL-C and remnant cholesterol, which are associated with increased CVD risk. A decrease of >20% in these variables from baseline to Week 16 was observed in higher proportions of the Saroglitazar Magnesium groups (1 mg, 2 mg, and 4 mg) and in a dose-dependent manner compared to placebo, with Saroglitazar Magnesium 4 mg having the greatest beneficial effect.

In the US, a Phase 2 study of 24 weeks duration was conducted to evaluate the safety and efficacy of Saroglitazar Magnesium 2 mg and 4 mg compared to placebo in 16 adult subjects with biopsy proven NASH without cirrhosis[31]. For the study primary efficacy endpoint, the changes in NAS at week 24 were -1.9±1.57, -1.5±0.84, and -1.3±0.58 in Saroglitazar Magnesium 4 mg, Saroglitazar Magnesium 2 mg, and placebo groups, respectively. For the study secondary endpoints, Saroglitazar Magnesium 4 mg and 2 mg improved liver histology, liver parameters, lipid parameters, glycemic control, and insulin resistance parameters over a period of 24 weeks.

In India, a Phase 3 study of 52 weeks duration was conducted to evaluate the efficacy and safety of Saroglitazar Magnesium 4 mg compared to placebo in 102 adult subjects with biopsy proven NASH without cirrhosis (CTRI identifier: CTRI/2015/10/006236). For the study primary efficacy

endpoint, there was a statistically significant higher proportion of subjects with decrease in NAS ≥2 points spread across at least 2 of the NAS components without worsening of fibrosis at week 52 in Saroglitazar Magnesium 4 mg group (52.3%) compared to placebo group (23.5%) (p-value: 0.0427). For the study secondary efficacy endpoints, Saroglitazar Magnesium 4 mg significantly reduced mean score of hepatocyte ballooning, steatosis, and NAS from baseline to Week 52 (p-value <0.05). Saroglitazar Magnesium 4 mg also improved liver parameters and lipid parameters from baseline to Week 52.

Other Indications:

Several clinical trials were conducted to evaluate the safety and efficacy of Saroglitazar Magnesium in dyslipidemic participants with and without diabetes, participants with impaired glucose tolerance test in India are summarized below.

A Phase 3 study of 24-week duration was conducted in 122 subjects to evaluate the efficacy and safety of Saroglitazar Magnesium in diabetic dyslipidemic patients compared to pioglitazone. There was a statistically significant reduction in the TG levels at all visits compared to baseline in Saroglitazar Magnesium 2 mg and 4 mg groups. There was a statistically significant reduction in the TG levels from baseline to Week 24 in Saroglitazar Magnesium 4 mg (45%) compared to pioglitazone 45 mg (15.5%)[32].

A Phase 3 study of 12-week duration was conducted in 302 subjects to evaluate the efficacy and safety of Saroglitazar Magnesium in diabetic dyslipidemic patients not controlled with atorvastatin 10 mg. There was a statistically significant reduction in TG levels from baseline to Week 12 in Saroglitazar Magnesium 2 mg and 4 mg groups (> 45%) compared to Placebo. There was also a statistically significant reduction from baseline to Week 12 in LDL-C (>27.5%), total cholesterol (>22%), and Apo B (>27%) levels in Saroglitazar Magnesium 2 mg and 4 mg[33].

A Phase 3 study of 56-week duration was conducted to evaluate the efficacy and safety of Saroglitazar Magnesium 2 mg and 4 mg as compared to pioglitazone 30 mg in 1155 adults with type 2 diabetes mellitus. The results showed that Saroglitazar Magnesium (2 mg and 4 mg) and pioglitazone 30 mg significantly reduce glycosylated hemoglobin (HbA1c), as compared to baseline after 24 weeks of treatment. In addition, Saroglitazar Magnesium (2 mg and 4 mg) and pioglitazone 30 mg significantly reduce HbA1c, as compared to baseline after 12 and 56 weeks of treatment. In this study, no significant safety findings were reported which were related to Saroglitazar Magnesium[35].

5.4 BENEFIT/RISK ASSESSMENT

NAFLD is considered to be the hepatic component of the metabolic syndrome, which includes dyslipidemia, peripheral insulin resistance, obesity, T2DM, and hypertension. Due to rising prevalence of obesity, T2DM, and hypertension, NAFLD has emerged as a major public health threat worldwide. Participants with NAFLD are more likely to die from CVD compared to

liver-related death. Therefore, the ideal drug to treat NAFLD/NASH should reduce the risk of CVD along with improving liver parameters and liver histology.

The safety and tolerability of Saroglitazar Magnesium is well defined based on pre-clinical and clinical trials (Phase 1 to Phase 3)[26, 30, 34]. [redacted]. Overall, Saroglitazar Magnesium has a favorable safety profile. Considering the efficacy results of pre-clinical and clinical trials, Saroglitazar Magnesium can improve lipid parameters and glycemic parameters including insulin resistance in patients with dyslipidemia. Moreover, Saroglitazar Magnesium has shown promising results in pre-clinical and clinical trials of Saroglitazar Magnesium in patients with NAFLD/NASH[26, 34, 30]. In pre-clinical trials, Saroglitazar Magnesium reduced hepatic steatosis, prevented development of fibrosis and reduced ALT and AST.

In a Phase 2 clinical study, Saroglitazar Magnesium significantly reduced ALT from baseline to Week-12[29]. In a Phase 3 study, Saroglitazar Magnesium 4 mg showed statistically significant reduction in proportion of subjects with decrease in NAS ≥2 spread across at least 2 of the NAS components without worsening of fibrosis, reduced mean score of steatosis, lobular inflammation, and hepatocyte ballooning, also reduced AST, ALT, ALP, and GGT without significant safety findings (preliminary unpublished results). Saroglitazar could reduce the risk of cardiovascular diseases along with improving liver parameters and liver histology in participants with NASH. Recently (March 2020), Saroglitazar has also received approval for marketing for treatment of non-cirrhotic nonalcoholic steatohepatitis in India. Therefore, the available information on Saroglitazar Magnesium suggests a favorable risk-benefit ratio.

The benefit-risk analysis evaluation has not revealed any significant risks that have an impact on the existing efficacy and safety profile of Saroglitazar Magnesium. Based on the assessment of all the safety issues and the benefits; the benefit-risk assessment was considered to remain favorable and unchanged.

More detailed information about the known and expected benefits and risks of Saroglitazar Magnesium may be found in the Investigator's Brochure.[29]

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary objective	Primary endpoint
To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in hepatic fat content measured by MRI Proton Density Fat fraction (MRI PDFF)	Change from baseline in hepatic fat content at Week 24/EOT
Secondary objectives	**Secondary endpoints**
1) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on improvement of hepatic fat content as measured by MRI PDFF.	1) Proportion of participants with reduction of at least 30% in hepatic fat content from baseline to Week 24/EOT
2) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in FibroScan®/VCTE .	2a) Change from baseline in LSM at Week 24/EOT. 2b) Change from baseline in continuous CAP at Week 24/EOT. 2c) Change from baseline in FAST score at Week 24/EOT
3) To evaluate the effects of Saroglitazar Magnesium 4 mg compared with Placebo on changes in non-invasive markers of fibrosis and steatosis	3a) Change from baseline in plasma pro-collagen type 3 (PRO-C3) levels at Week 24/EOT. 3b) Change from baseline in Fibrois-4 index (FIB-4), AST to Platelet Ratio Index (APRI) and Nonalcoholic fatty liver disease Fibrosis Score (NFS) at Week 24/EOT
4) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on liver enzyme, lipid profile, and fasting glucose	4a) Change from baseline in liver enzyme parameters (ALT and AST) at Week 24/EOT. 4b) Change from baseline in triglyceride [TG],, high-density lipoprotein [HDL], low-density lipoprotein [LDL], very low-density lipoprotein [VLDL], total cholesterol, and non-HDL cholesterol at Week 24/EOT. 4c) Change from baseline in fasting plasma glucose (FPG)at Week 24/EOT.
5) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on anthropometric measurements.	5) Change from baseline in body weight, BMI, hip circumference, and minimum waist circumference at Week 24/EOT
6) To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in Health-related quality of life scores measured by Short Form-36 (SF-36) Questionnaire.	6) Change from baseline in SF-36 Questionnaire mental (MCS) and physical components scores (PCS) at Week 24/EOT.
Safety objectives	**Safety Assessments**
1) To evaluate the safety and tolerability of Saroglitazar Magnesium 4 mg compared with placebo.	1a) Frequency and severity of TEAEs, SAEs, and AESI 1b) Changes in clinical laboratory testing parameters (hematology, clinical chemistry, and urinalysis) 1c)Changes in vital signs (Blood pressure, Pulse rate, Respiratory rates, Temperature) 1d) Changes in physical examination assessments
Exploratory Objectives	**Exploratory Endpoints**
1. To evaluate the effects of Saroglitazar Magnesium 4 mg compared with Placebo on lipid and glycemic markers	1a) Change from baseline in C-peptide at Week 24/EOT 1b) Change from baseline in Insulin, HbA1c, and TG/HDL ratio at Week 24/EOT 1c) Change from baseline in Free fatty acids at Week 24/EOT

	1d) Change from baseline in NMR lipoprofile at Week 24/EOT 1e) Change from baseline in enhanced liver fibrosis (ELF) score at Week 24/EOT

7. STUDY POPULATION

7.1 NUMBER OF PARTICIPANTS PLANNED

It is planned to enroll approximately 120 participants with NAFLD in People Living with HIV in this study. Participants with NAFLD who meet the eligibility criteria will be randomized in a 1:1 ratio to receive Saroglitazar Magnesium 4 mg or Placebo once daily orally for 24 weeks.

7.2 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Adults (≥18 years of age) with documented HIV.
2. Documented diagnosis of NAFLD established by imaging (ultrasound, CT scan or MRI) or liver biopsy within 6 months before screening, based on American Association for the Study of Liver Disease [AASLD] criteria
3. Hepatic fat fraction ≥8% by MRI-PDFF
4. ALT level ≥31 U/L in men and ≥19 U/L in women at Visit 1 and 2
5. HIV-1 RNA <200 copies/mL for ≥6 months on ART (must have screening HIV-1 RNA value and one clinical care value within 6 months prior to screening and up to the randomization that meets the criteria).
6. Stable ART regimen for ≥3 months prior to screening and stable up to the randomization and no active plans to change ART while on study.
7. Willingness to participate in the study.

7.3 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1) History of significant alcohol consumption (defined as >2 drinks/day on average for men, >1 drinks/day on average for women) for at least 3 consecutive months (12 consecutive weeks) within 5 year before screening (Note 1: 1 drink =12 ounces of beer, 8-9 ounces of malt liquor, 4 ounces of wine or 1 ounce of spirits/hard liquor. Note 2: Use sex assigned at birth for alcohol consumption limits).
2) History of other acute or chronic liver disease, including, but not limited to autoimmune, primary biliary cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis, hepatitis B virus (HBV), and ongoing or recent (within the past 3 years) hepatitis C RNA positivity. (Exceptions: a. Participants with previously treated hepatitis C infection are eligible for consideration if their sustained virologic response was achieved more than 3 years prior to screening. The proportion of such participants in this trial will not exceed 25% of the study cohort. b. Participants with prior acute HBV infection that is resolved but currently do not have hepatitis B surface antigen (HBsAg) or detectable HBV DNA are eligible).

3) History of liver transplant.
4) Liver biopsy or radiologic imaging consistent with the clinical presence of cirrhosis or portal hypertension at screening.
5) Participants whose Visit 2 ALT, AST, or alkaline phosphatase (ALP) values exceed their Visit 1 values by more than 50%.

   Note: These participants will be required to have a third value measured at-least one week after V2, to assess for a trend. If the third value shows a continued increase ≥10% compared to the Visit 2 values, the participant is considered ineligible for randomization.

6) Ongoing use of steatogenic medications or supra-physiologic hormonal therapies (Exception: transgender women on stable (≥3 month) feminizing hormonal therapy not excluded), within 3 months prior to screening until time of randomization or anticipated use of medications that cause significant changes in weight during the study period (Refer Appendix 7 for 'List of Steatogenic Medications Or Supra-Physiologic Hormonal Therapies Or Medications That Cause Significant Weight Change').
7) Uncontrolled T2DM, defined as HbA1c >9.5% at screening.
8) Any of the following laboratory values at screening:

   a. ALT or AST >250 U/L
   b. Total bilirubin >1.5 mg/dL and direct bilirubin > 0.5 mg/dL (unless due to Gilbert's disease or atazanavir use per the opinion of the site investigator)
   c. Platelet count <150,000/mm^3
   d. Estimated glomerular filtration rate (e-GFR) <60 mL/min/1.73m^2 using the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation (Refer Appendix 6 for 'CKD-EPI Calculator')
   e. International normalized ratio (INR) >1.3.
   f. Albumin < 3.6 g/dL

9) History of malignancy in the past 5 years and/or active neoplasm with the exception of superficial, non-melanoma, skin cancer.
10) Unstable cardiovascular disease, including:
   a) Unstable angina, (i.e., new or worsening symptoms of coronary heart disease) and/or acute myocardial infarction within the 3 months preceding screening
   b) Acute coronary syndrome or coronary artery intervention within the 3 months preceding screening,
   c) Heart failure of New York Heart Association (NYHA) class (III-IV) or worsening congestive heart failure within the 6 months preceding screening.
   d) History of (within 3 months preceding screening) or current unstable cardiac dysrhythmias.
   e) Uncontrolled hypertension (systolic blood pressure [SBP] >155 mmHg and/or diastolic blood pressure [DBP] >95 mmHg) at screening.
   f) Stroke or transient ischemic attack within the 6 months preceding screening.

11) Unstable pulmonary disease (based upon site investigator's evaluation) at screening.
12) Use of drugs that are known CYP2C8 inhibitors/substrates (Refer Appendix 2 for the 'List of Known CYP2C8 Inhibitors/Substrates') in the last 28 days prior to screening.
13) History of severe illness or any other conditions that require systematic treatment/or hospitalization, until participant either completes therapy or is clinically stable on therapy as per the opinion of the investigator, for at least 7 days prior to screening (such as poorly controlled psychiatric disease, active gastrointestinal conditions that might interfere with drug absorption, etc.).
14) Use of thiazolidinediones or Telmisartan within 3 months prior to screening or until time of randomization.
15) Use of unstable doses of SGLT2 inhibitors (e.g. canagliflozin, empagliflozin, dapagliflozin, etc.), glucose-dependent insulinotropic polypeptide (GIP) and/or GLP-1 agonists (e.g. semaglutide, exenatide, liraglutide, lixisenatide, tirzepatide etc.) within 6 months prior to screening until time of randomization.
16) Use of pentoxifylline, ursodeoxycholic acid, antioxidants such as vitamin E (>200 IU/day), glutathione, orlistat, betaine, or non-prescribed complementary alternative medications within 6 months prior to screening until time of randomization.
17) Known allergy, sensitivity or intolerance to the study medication or formulation ingredients.
18) History of any known bleeding disorder or coagulopathy.
19) Any condition that in the opinion of the site investigator, would compromise the participant's ability to participate in the study.
20) Unstable doses of anti-diabetic agents including sulfonylureas, biguanides or DPP-4 inhibitors in the last 3 months prior to screening until time of randomization.
21) Unstable doses of lipid lowering agents such as statins (e.g. simvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin, etc.) or fibrates (clofibrate, Fenofibrate) in the last 3 months prior to screening until time of randomization.
22) Participant with weight change >5% within 6 months prior to screening until time of randomization.
23) History of bariatric surgery or currently undergoing evaluation for bariatric surgery.
24) Participation in another interventional clinical study and/or receipt of any other investigational medication within 3 months prior to screening.
25) History of COVID-19 infection in the last 30 days prior to screening.
26) Pregnancy-related exclusions, include:
    a. Pregnant/lactating female (including positive pregnancy test at screening)
    b. Pregnancy should be avoided by male and female participants either by complete abstinence or the use of acceptable effective contraceptive measures for the duration of the study and for at least 1 month after the end of the study treatment. Refer Appendix 3 Contraceptive Guidance
27. Participants having an absolute contraindication to MRI (eg., any implants, magnetic metals, cardiac pacemakers, neurostimulator) as per investigators' discretion

7.4 PARTICIPANT WITHDRAWAL

A participant may withdraw from the study at any time without penalty and for any reason without prejudice to her/his future medical care. Although a participant is not obliged to give his/her reason for withdrawing prematurely, the investigator will make a reasonable effort to obtain the reason while fully respecting the participant's rights. If there is a medical reason for withdrawal, the participant will remain under the supervision of the investigator for follow-up of AE(s) as detailed in Section 12.4.1.6.

Every effort will be made to continue clinical and/or laboratory follow-up, as appropriate, in participants who wish to withdraw from the study medication, and reasonable efforts will be made to contact a participant who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health. A participant's withdrawal of consent and agreement to undergo a final examination will be documented on the case report form (CRF) and on the investigator's copy of the informed consent form (ICF), which will be countersigned and dated by the participant. Safety follow-up within 4 weeks from the date of withdrawal will be conducted for all participants who receive the study medication but do not complete the study according to the study protocol.

7.5 Screen Failure

A screen failure occurs when a participant who has signed the ICF does not meet all the entry criteria outlined in this protocol and has not been randomized.

Participants who fail to meet all the screening criteria will not be rescreened unless approved by the sponsor or its designee in writing. Screening laboratory tests may be repeated once following the approval of the sponsor or its designee, if the laboratory test results seem implausible or inaccurate. No study procedures (including safety follow-up) will be performed for these participants.

For participants who fail to meet the inclusion criteria or who meet at least one of the exclusion criteria, the investigator (or designee) will document on a screening form the reason for the screening failure.

7.6 DISCONTINUATION OF PARTICIPANTS FROM THE STUDY AND STUDY DRUG

7.6.1 Discontinuation of Study Drug

7.6.1.1. Discontinuation Due to AE/SAE

The following clinical events warrant discontinuation of the study drug; however, the participant will continue to be followed for safety, and the relevant laboratory tests will be performed until

the event has resolved, i.e., clinical laboratory value(s) has/have returned to baseline or is/are no longer of clinical significance.

- Any AE (CTCAE, Version 5.0 or higher) of Grade ≥3 that is possibly or likely study drug-related
- Any AE of CTCAE Grade ≥ 4 regardless of attribution to the study drug.
- SAE that may be related to the study drug may warrant discontinuation, as per the discretion of the site investigator.
- In the opinion of the site investigator, continuation of the study drug poses a health risk to the participant

7.6.1.2 Drug Induced Liver Injury & Liver Function Monitoring

Monitoring of DILI will be done during this study as per Tables 1 and 2:

A separate blinded HSAC will be established. The committee will review, monitor and adjudicate possible cases of DILI in the study (refer to Section 12.4.3).

(Note: Prior to using these tables, R ratio would be calculated as alanine aminotransferase (ALT)/ALT upper limit of normal (ULN) divided by alkaline phosphatase (ALP)/ALP ULN (ALT/ULN÷ALP/ULN).

Table 1. Algorithm for Monitoring and Management of Elevated ALT in Participants with Normal or Elevated Baseline ALT[a]

Treatment emergent ALT elevations	Treatment emergent total bilirubin elevations	Liver-related Symptoms (as a variable)	Action[b]
Normal/near normal baseline[a]: ALT ≥5x ULN Elevated baseline [a]: ALT ≥3x baseline or ≥300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome: No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
Normal/near normal baseline[a]: ALT ≥3x ULN Elevated baseline[a]: ALT ≥2x baseline or ≥300 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome: No change in baseline TBL	Severe fatigue, nausea, vomiting, right upper quadrant pain	Repeat ALT, AST, ALP, TBL, in 2-5 days. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
Normal/near normal baseline[a] ALT ≥8 x ULN Elevated baseline[a]: ALT ≥5x baseline or ≥500 U/L (whichever occurs first)	Normal Participants with Gilbert's syndrome: No change in baseline TBL	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Normal/near normal baseline[a]: ALT ≥3x ULN Elevated baseline[a]: ALT ≥2x baseline or ≥300 U/L (whichever occurs first)	TBL ≥2x ULN Participants with Gilbert's syndrome: Doubling of direct bilirubin or increased INR to >1.5	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Normal/near normal baseline [a]: ALT ≥5x ULN Elevated baseline [a]: ALT ≥3x baseline or ≥300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin, ULN= upper limit of normal.

Modified from Chalasani N, Regev A. Drug-induced liver injury in participants with pre-existing chronic liver disease in drug development: how to identify and manage? Gastroenterology. 2016;151:1046-1051.

[a]Elevated baseline is defined as ALT ≥1.5x ULN. Normal/near normal baseline is defined as ALT < 1.5x ULN. In participants with a sizable stable decrease in ALT (>50% of the baseline value) during treatment, a new baseline, corresponding to the ALT nadir, should be established on an individual basis for subsequent determination of a DILI signal.

[b]The actions of close observation, monitoring, and drug interruption often overlap. Occasionally, workup is initiated after drug interruption.

Table 2. Detection and monitoring of elevated serum alkaline phosphatase

Treatment Emergent Serum Alkaline Phosphatase (ALP) elevations	Serum Total Bilirubin	Action/Follow-up
>2 times upper limit of normal (ULN) or > 250 IU/L whichever comes first, (unless ALP not of hepatic origin)	Within normal range	• Work up for cholestasis • Repeat liver profile within one week • If there is progressive increase in ALP (e.g. increase by 50% from previous value) or there is associated doubling of direct bilirubin + exceeds ULN, interrupt the investigational product • Restart the investigational product only if a competing etiology is identified and ALP is returning close to baseline
>2 times ULN	≥ 2 times ULN or In case of pre-existing Gilbert's, doubling of direct bilirubin + exceeding ULN	• Work up for cholestasis • Interrupt the investigational product • Repeat liver profile within 2-3 days • Restart the investigational product only if a competing etiology is identified and ALP is returning close to baseline
1-2 times ULN	>3 mg/dl or In case of pre-existing Gilbert's, doubling of direct bilirubin + exceeding ULN	• Work up for cholestasis • Interrupt the investigational product • Repeat liver profile within 2-3 days • Restart the investigational product only if a competing etiology is identified and ALP is returning close to baseline

7.6.1.3 Temporarily interrupting the study drug for important biological considerations:

- Total CPK >5x ULN (if normal at baseline), or >5x baseline (if elevated at baseline)
- Total CPK >3 x ULN (if normal at baseline) or >3x baseline (if elevated at baseline) associated with:
    a. Elevation for more than 2 weeks OR
    b. Symptoms concerning for rhabdomyolysis/myositis.
- Estimated glomerular filtration rate (e-GFR; calculated from CKD-EPI Equation) ≤40 mL/min/1.73 m^2 and where the value is reconfirmed between 24 to 72 hours from the time the site is made aware of the initial results Additionally, any participant who requires renal replacement therapy for any reason should also be discontinued from the study medication.
- Complete blood counts (CBCs): hemoglobin <10 g/dL; platelets <100,000/µL; and absolute neutrophil count <1,000 /µL.

7.6.2 Discontinuation of Participant From the Study

A study completion CRF, which includes the reason for discontinuation, must be completed for all participant who are discontinued from the study. If the participant is discontinued

prematurely, the study completion CRF should clearly indicate the reason for discontinuation. If the participant discontinues due to an AE, an AE CRF must be completed.

1. Participant's decision to withdraw consent for trial participation: In case of withdrawal of consent and unless otherwise stated by the participant in the withdrawal of consent, investigator will be encouraged to obtain information from the participant in order to follow the medical status of the participants (especially when the participant withdraws his/her consent after having experienced an AE/SAE or an efficacy endpoint). Principal Investigator or designee(s) must make reasonable attempts to contact participants that are lost to follow-up, in order to obtain health status and reason for withdrawal. These attempts must be documented in the study forms.
2. Noncompliance to the protocol requirements, including any major deviation which may influence the results/outcome of primary endpoint or participant safety.
3. Either the investigator or the sponsor decides that discontinuing the participant from the study is in the participant's best interest.
4. A participant may also be discontinued from the study by the regulatory authorities or institutional review board (IRB).
5. If the participant becomes pregnant, as specified in Section 12.4.5.

7.6.3 Lost to Follow-up

Principal Investigator or designee(s) must make reasonable attempts to contact participants that are lost to follow-up, in order to obtain health status and reason for withdrawal. These attempts must be documented in the study forms.

7.6.4 Discontinuation of Trial

If the Investigator, the Sponsor or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. Also, the clinical study may be terminated at the Sponsor's discretion in the absence of such a finding. Should the study be terminated and/or the site closed for whatever reason, a copy of all documentation pertaining to the study and the study medication must be returned to the Sponsor. All site-specific documents will be archived at study site.

8. STUDY TREATMENTS/INVESTIGATIONAL PRODUCT (IP) MANAGEMENT

The participant will be instructed to take one Saroglitazar Magnesium 4 mg or Placebo tablet once daily in the morning before breakfast without food for a period of 24 weeks.

8.1 TREATMENTS TO BE COMPARED

8.1.1 Investigational Product Description

The IPs that will be used in this study are outlined in Table 3.

Table 3: Identity of Study Drugs

Study Drug	Formulation	Strength	Route	Manufacturer
Saroglitazar Magnesium	Tablet	4 mg	Oral	[redacted]
Placebo	Tablet	Matching Placebo	Oral	[redacted]

Source: Investigator's Brochure[26]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]		[redacted]	
		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]*
***Round-up quantity**					

8.1.2 Comparator Drug Description

Placebo will be used as comparator, which will be formulated as identical appearing tablets, and will contain all the excipients mentioned in Table 4, except Saroglitazar Magnesium. The IP will be manufactured following pharmaceutical grade cGMP guidelines.

8.2 DOSAGE AND TREATMENT SCHEDULE

Participants will ingest either Saroglitazar Magnesium 4 mg or Placebo orally once each morning before breakfast without food for a period of 24 weeks.

However, on every scheduled clinical visit, participants will be instructed not to take the IP until after fasting blood sample collection.

8.3 PACKAGING, LABELLING AND SUPPLY

The study medication will be packaged by the sponsor according to all the local legal requirements. [redacted]

[redacted]

An adequate quantity of the study medication will be shipped to each site. The site's investigational drug pharmacy will maintain an accurate record of the receipt of the study medication, including the date received. Until dispensed to the participants, the study medication will be stored at room temperature (20°C to 25°C or 68°F to 77°F) in a dry place at the study site or pharmacy in a secure locked area and that is accessible to authorized personnel only.

8.4 STORAGE CONDITIONS

Investigational products will be stored at room temperature (20°C to 25°C or 68°F to 77°F) in a dry place excursions permitted to 15-30°C (59-86°F) at the study site or pharmacy. If the IP temperature extends outside the 20°C to 25°C range, a temperature excursion must be documented in the study-specific temperature log, and sent to the sponsor. If the excursion is within 15°C to 30°C (59ºF to 86ºF), quarantine is not required, and the IP is acceptable for use. If the excursion is outside of the 15°C to 30°C range, the IP must be quarantined until a decision on the stability of the IP is made by the sponsor. If the excursion goes beyond the range of 15°C to 30^0 C, it will be considered as a protocol deviation. All IP supplies in the study will be stored at the study site or pharmacy in a secure locked area that is accessible to authorized personnel only. Participants should store the study medication at 25°C (77°F) with excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Keep container tightly closed.

8.5 BLINDING/UNBLINDING

The study will be performed in a double-blind manner. All study medication will be supplied in identical packages and study medication bottles. The study medication tablets will be similar in color, smell, taste, and appearance, thereby maintaining double-blind conditions.

The intent of blinding is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. The essential aim of blinding, therefore, is to prevent identification of the treatments by the investigator, participant, 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, biostatisticians who are directly involved in the analysis of the study results will remain blinded to treatment assignment while the study is in progress. For the purposes of Data and Safety Monitoring Board (DSMB) review, a separate unblinded statistician will be utilized; further details will be included in the DSMB Charter.

In case a participant experiences an AE, which meets the criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements

or in the event of a medical emergency during the study where the knowledge of participant treatment is required, the investigator will unblind the treatment assignment for a specific participant via IWRS. In this event, neither the Sponsor representatives nor any other study personnel will have access to the treatment code. This level of blinding will be maintained throughout the conduct of the study. The Investigator should notify the Sponsor prior to unblinding a participant if there is sufficient time. Further, the Sponsor must be informed whenever the randomization code is broken and the reasons for unblinding.

8.6 METHOD OF ASSIGNING PARTICIPANT TO TREATMENT GROUP

Participants will be 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. This scheme will ensure that the two groups will be balanced by calendar time of enrollment (to minimize secular effects) and by clinic (to minimize clinic-specific effects of differences in patient populations and management).

The randomization scheme will be prepared by an unblinded statistician or designee. Requests for randomizations will be made by the clinics using IWRS (Interactive Web Response System). An assignment will be issued only if the database shows that the patient is eligible, has signed the consent statement, and has had all required baseline data keyed into the database.

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 will be generated using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA).

8.7 SELECTION OF DOSES

Saroglitazar Magnesium 4 mg has been selected for this study based on previous pharmacokinetics, dose ranging studies, HIV lipodystrophy study, and two published studies in primary NAFLD[30, 31].

8.8 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

8.8.1 Previous and Concomitant Medications

Any medication the participant takes, other than the study drug, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications and any changes in the dosage or regimen of a concomitant medication for the 6 months preceding Visit 1 (screening visit) until the end of the study (i.e., the safety follow-up visit-12) must be recorded in the CRF.

8.8.2 Permitted Concomitant Medication:

- With the exception of prohibited concomitant medications, the following medications that the participants have been taking at stable dosages for at least 3 months before screening (Visit 1) until the end of study will be permitted as concomitant medications:

  - Lipid-lowering drugs- statins and fibrates,
  - Anti-hypertensives
  - Stable ART regimen.

- The SGLT2 inhibitors (e.g. canagliflozin, empagliflozin, dapagliflozin, etc.), glucose-dependent insulinotropic polypeptide (GIP) and/or GLP-1 agonists (e.g. semaglutide, exenatide, liraglutide, lixisenatide, tirzepatide etc.) that the participants have been taking stable doses for at least 6 months before screening (Visit 1) until the end of study
- Antidiabetic medications i.e., metformin, sulfonylureas, insulin, dipeptidyl peptidase 4 inhibitors (gliptins) will be permitted if the dose has been stable for 3 months prior to screening (visit 1) until the end of study
- In case of further adjustment of anti-diabetic treatment is needed during the study, the following guidance should be exercised in line with local standard practice as considered appropriate by treating physician:
  - Maximizing doses of metformin, dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors or gliptins), sulfonylurea (excluding those more prone to induce hypoglycemia).
  - For participants receiving SGLT2 inhibitors, GIP and/or GLP1-RAs at screening, it is recommended to avoid increase in dose of SGLT2 inhibitors, GIP and/or GLP1 RAs throughout study.
  - For participants not receiving SGLT2 inhibitors, GIP and/or GLP1-RAs at screening, treatment with SGLT2 inhibitors, GIP and/or GLP1-RAs should not be started throughout study.
- The Investigator at his/her discretion will also be allowed to offer a rescue medication for clinically significant conditions correlated with the laboratory findings, if required, however, such interventions shall be recorded in the eCRF with description of type of intervention, dose and duration. Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for prohibited medications listed in Section 8.8.3. If medication given is in violation to the protocol, then such subjects will be withdrawn from the trial. Allowed over-the-counter medications (OTC) such as acetaminophen (maximum 1 gram/day), ibuprofen (maximum 800 mg/day), naproxen (maximum 440 mg/day), antacids such as H2 receptor blockers, and proton-pump inhibitors for shorter duration (up to 14 days) as per the investigator's discretion. Participants will also be instructed about the importance of not

taking any other medication throughout the study (including OTC medications) without consulting the Investigator.

- The stable doses of allowed concomitant medications should not be changed either at/between the screening visits or at randomization visit. Upon randomization of participants, they will be discouraged from making any changes in allowed concomitant medications and encouraged to make alternative options. However, the site investigator at his/her discretion can modify the dose of the current regimen or change any permitted medication to another permitted medication if clinically indicated.
- The site investigator should be alerted if, during the course of the study, a participant requires a new medicine or therapy or a change to an established dosing regimen. All medications that target NAFLD or NASH, or have been suggested to target the underlying causes of NAFLD or NASH, should be reviewed and agreed upon by the Investigator and Sponsor's representatives including Medical Expert/Medical monitor before being taken by the participant.

8.8.3 Prohibited Concomitant Medications

Participants are not permitted to take the following medications during the study period/until the end of the study.

- Parenteral nutrition and Vitamin E (>200 IU/day). Increase in dose of Vitamin E is not allowed throughout the study
- Other drugs with potential effects on NAFLD, such as ursodeoxycholic acid, pentoxifylline, glutathione, orlistat, betaine, or non-prescribed complementary alternative medications 6 months prior to screening until the end of the study.
- Thiazolidinediones, telmisartan 3 months prior to screening until the end of the study.
- Chemotherapy.
- Other investigational medications 3 months prior to screening until the end of the study.
- Any medication that causes hepatic steatosis (e.g., amiodarone, tamoxifen, methotrexate, systemic glucocorticoids, anabolic steroids, tetracycline, estrogens in doses higher than used in oral contraceptives or post-menopausal hormone replacement therapy [except for transgender women on stable dosing], vitamin A, L-asparaginase, valproate, chloroquine, stavudine) 3 months prior to screening until the end of the study.
- Known CYP2C8 inhibitors/substrates (Refer Appendix 2 for the 'List of Known CYP2C8 Inhibitors/Substrates') 4 weeks prior to screening until the end of the study.

8.8.4 Other Restrictions

8.8.4.1 Alcohol

Participants are encouraged to stop alcohol consumption entirely during the study. Details of alcohol consumption will be evaluated through the AUDIT questionnaire throughout the study period (Refer Appendix 5) (Note: 1 unit = 12 ounces of beer, 4 ounces of wine or 1 ounce of spirits/hard liquor.

8.8.4.2 Diet and Exercise

Participants are encouraged to maintain lifestyle modifications, including diet and exercise, previously undertaken (Refer Appendix 8). Participants should make no major changes in the type or amount of exercise in which they take during the study.

8.9 OVERDOSE AND DRUG INTERACTION

No incidence of overdose with Saroglitazar Magnesium has been reported. In case of overdose with Saroglitazar Magnesium, general supportive care of the participant is indicated, including monitoring of vital signs and observation of clinical status.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.10 TREATMENT COMPLIANCE

Participants will be instructed by study personnel/coordinator on the importance of being compliant with the use of the study drug throughout the clinical trial. At each study visit, previously dispensed unused study drug will be retrieved by the study personnel/coordinator from respective

participant and compliance will be assessed. Compliance will be also documented by recording the number of tablets dispensed, number of tablets consumed by participant, the number of tablets missed, if any, and number of tablets returned back to study personnel/coordinator since the last study visit. If treatment is interrupted, whatever the cause, duration, and reason of the interruption should be documented appropriately in source records. Although 100% compliance to study medication is desired and should be encouraged throughout the treatment phase, a compliance of ≥80% and ≤120% over a total duration of treatment will be considered acceptable.

9. OBSERVATIONS

9.1 CRITERIA FOR SAFETY

Safety will be assessed at each scheduled visit and assessment will include AEs/SAE, clinical laboratory tests, vital signs, physical examination, and body weight assessment.

9.1.1 Safety and Tolerability Variables

The following safety assessments will be evaluated through the study period:

1. Frequency and severity of treatment-emergent AEs (TEAEs, including treatment-emergent serious AEs [TESAEs], TEAE leading to discontinuation, TEAE related to IP, AE of special interest [DILI, and weight gain], and SUSARs).
2. Changes in physical examination
3. Changes in vital signs.
4. Changes in laboratory parameters

9.1.2 Medical History and Demographic Information

The medical history comprises:

- General medical history.
- Medication history.
- Alcohol history.

The following demographic information will be recorded:

- Gender.
- Age.
- Ethnicity.
- Race.

9.1.3 Clinical Laboratory Assessments

9.1.3.1 Sample Collection

Blood samples will be collected for clinical laboratory testing at the time points indicated in the Section 2 Schedule of Assessments. . All laboratory investigations will be performed with at least 8-hours fasting blood samples. Safety laboratory variables are listed below:

1. CBC includes hemoglobin, white blood cell count with differential, absolute neutrophil count (ANC), red blood cell count, platelet count, mean corpuscular volume, and hematocrit.
2. INR.
3. CMP includes potassium, sodium, chloride, serum bicarbonate, calcium, phosphate, blood urea nitrogen (BUN), creatinine, uric acid, glucose, total protein, and LFT (ALT, AST, ALP, bilirubin [total, direct, and indirect bilirubin], and serum albumin).

4. e-GFR (will be calculated by CKD-EPI equation using creatinine value from CMP, refer Appendix 6).
5. CPK.
6. Urine Analysis:

- Urine Chemical Examinations: pH, specific gravity, protein, glucose, bilirubin, ketone bodies, and nitrite
- Urine Microscopy: epithelial cells, RBCs, pus cells, cast, and crystals.
- Lipid profile includes TG, HDL, LDL, VLDL, TC, and non-HDL-C

9.1.3.2 Urine and Serum Pregnancy Tests

Urine and serum pregnancy test (participants of child-bearing potential) will be processed by a local laboratory during all scheduled visits (Section 2 Schedule of Assessments).

9.1.3.3 Vital Signs

The following vital signs will be assessed at time points described in the Schedule of Assessments (Section 2):

- Sitting SBP and DBP (mmHg).
- Heart rate (pulse) (beats per minute).
- Body temperature (°F).
- Respiratory rate (breaths per minute).

Vital signs will be measured before any blood draw that occurs at the same visit and after the participant has been resting for at least 5 minutes.

9.1.3.4 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Assessments (Section 2). Participants' body weight (standing scale) will be recorded during all physical examinations. The extremities will be examined for any signs of edema in complete and targeted physical examination. Height will be recorded at Screening Visit only. Standardized hip circumference and minimum waist circumference (Refer Appendix 9) will be measured, as per time points mentioned in the Schedule of Assessments.

9.2 EFFICACY

9.2.1 Primary Endpoint

Change from baseline in hepatic fat content at Week 24/EOT

9.2.2 Secondary endpoints

The following secondary efficacy endpoints will be evaluated from baseline to end-of-treatment (Week 24):

1. Proportion of participants with reduction of at least 30% in hepatic fat content from baseline to 24 week/EOT
2. Change from baseline in LSM, CAP, and FAST score at Week 24/EOT.
3. Change from baseline in enhanced liver fibrosis score at Week 24/EOT.
4. Change from baseline in PRO-C3 levels at Week 24/EOT.
5. Change from baseline in FIB-4, APRI and NFS at Week 24/EOT.
6. Change from baseline in liver enzyme parameters (ALT and AST levels) at Week 24/EOT.
7. Change from baseline in TG, HDL, LDL, VLDL, total cholesterol, and non-HDL cholesterol at Week 24/EOT.
8. Change from baseline in fasting plasma glucose at Week 24/EOT.
9. Change from baseline in body weight, BMI, hip circumference, and minimum waist circumference at Week 24/EOT.
10. Change from baseline in SF-36 Questionnaire mental and physical component scores at Week 24/EOT

9.2.3 Exploratory Endpoints

1. Change from baseline in C-peptide at Week 24/EOT
2. Change from baseline in Insulin, HbA1c, and TG/HDL ratio at Week 24/EOT
3. Change from baseline in Free fatty acids at Week 24/EOT
4. Change from baseline in NMR lipoprofile at Week 24/EOT
5. Change from baseline in ELF levels at Week 24/EOT

9.2.4 Health-related Quality of Life (HR-QoL)

Subjective HR-QoL assessments will be measured using the SF-36 Version 2.0 (See Appendix 4), which is a 36-item patient response questionnaire that measures HR-QoL across 8 domains, which has both physical and emotional based components. The 8 domains are physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

9.2.5 VCTE/FibroScan®

Liver stiffness measurements will be performed by VCTE using the FibroScan as per time points mentioned in the Schedule of Assessments (Section 2). The appropriate FibroScan measurement probe should be used based on the manufacturer's recommendation for probe choice according to chest circumference and age.

VCTE/FibroScan® procedure will be performed based on institutional practice. The VCTE/FibroScan® exam will only be considered acceptable if it results in 12 (or based on institutional practice) measurements with a 70% success rate, and the interquartile range for liver stiffness measurement (LSM) is less than 30% of the value of the median. CAP will be simultaneously measured with LSM using the same probe.

9.2.6 Blood Samples

Multiple venipunctures should be avoided when collecting blood samples. It is recommended to collect blood sample for safety and efficacy measurement as per time points mentioned in the Schedule of Assessments (Section 2).

9.2.7 Total Amount of Blood

The total amount of blood drawn from each participant will not exceed 292 mL during the course of study.

9.2.8 Biospecimen Banking

Biospecimens for banking include plasma and serum. Approximately 86 mL of whole blood will be collected as per time points mentioned in the Schedule of Assessments (Section 2).

Biospecimens for banking also include optional collection of stool. This will be collected as per time points mentioned in the Schedule of Assessments (Section 2). The biospecimens will be shipped to the Indiana University Biorepository.

9.2.9 ELF score

Enhanced liver fibrosis score is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal pro-peptide of type III procollagen (PIIINP), and hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease. These biomarkers will be measured on the stored sample.

9.2.10 PRO-C3

PRO-C3 is the pro-peptide of type III collagen and it is an accurate biomarker for the formation of fibrotic tissue in the liver. Type III collagen is one of the most abundant proteins in fibrotic tissue and is a reliable biomarker for liver fibrosis. These biomarkers will be measured on the stored sample.

9.2.11 NFS

The NFS is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio) and is calculated using the published formula. A score 0.676 had 67% sensitivity and 97% specificity to identify the presence of advanced fibrosis.

Formula: -1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × Platelet (× 10^9 /L) – 0.66 × Albumin (g/dL).

It will be calculated at Weeks 4, 12, and 24/EOT.

9.2.12 FIB-4 index

FIB-4 index is an algorithm based on platelet count, age, AST, and ALT that offers dual cut-off values (participants with score 3.25 are likely to have advanced fibrosis).

Formula: Age (years) × AST [U/L]/(Platelet [10^9/L] × ALT [U/L]$^{1/2}$).

It will be calculated at Weeks 4, 12, and 24/EOT.

9.2.13 APRI

Aspartate aminotransferase [AST] to platelet ratio index (APRI) is a non-invasive marker of advanced fibrosis in participants with NAFLD.

Formula: (AST [IU/L])/(AST upper limit of normal [IU/L])/(Platelet [10^9 /L]) × 100.

It will be calculated at Weeks 4, 12, and 24/EOT.

Microbiome Assessment

Stool specimens for microbiome assessment will be collected and stored in freezer at -80°C as per time points mentioned in the Schedule of Assessments (Section 2). Further metagenomics, transcriptomic, and metabolomics studies will be conducted as an ancillary study to the parent trial. Stool banking is optional and requires additional consent.

9.3 APPROPRIATENESS OF MEASUREMENT

The endpoints chosen for the given study (safety and efficacy) are appropriate for the assessment of the outcome of the study.

9.4 ABNORMAL LABORATORY FINDINGS

A clinically significant value outside the normal or reference range in a routine safety assessment, such as clinical laboratory, vital signs, may signify an AE finding. Additional examinations or repetition of test will be performed as medically indicated.

If the investigator considers the abnormality as of medical relevance, he/she should also record this as an AE. If the findings contribute to a clinical diagnosis (e.g. hepatitis in case of increased liver enzymes), this diagnosis should be recorded as an AE.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. The test result is associated with accompanying symptoms, and/or
2. The test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. The test result leads to change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. The test result leads to any of the outcomes included in the definition of an SAE, and/or
5. The test result is considered to be an AE by the investigator or designee.

For any abnormal test result that meets one of the above conditions except for the last condition, the investigator or designee will provide a justification in the source documentation for not reporting the abnormal test finding as an AE.

Each AE shall be evaluated for the severity, seriousness, duration, resolution, action taken, and its association with the study medication. The study participant may be withdrawn or terminated from the study depending on the seriousness of the AE(s).

10. INVESTIGATIONAL PLAN

10.1 TRIAL DESIGN AND PLAN

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. Eligible participants will be randomized in a 1:1 ratio to receive Saroglitazar Magnesium 4 mg or placebo. This study plans to enroll approximately 120 PLWH with NAFLD from within the catchment area of approximately 8 participating clinical centers or community HIV practices in US. The study will be conducted over a period of 36 weeks, including upto 8-week screening period, 24-week treatment period and 4-week safety follow-up period (Figure 1 and Section 2 Schedule of Assessments). Participants will be evaluated at the study sites for 10 scheduled visits.

- Screening: Week -8 (Visit 1) and Week -6 (Visit 2); Screening period will last up to 8 weeks. Visit 2 must occur at least 14 days after Visit 1.
- Randomization: Day 1 (Visit 3) can occur at any time point after visit 2 but within 8 weeks of screening period and participant can be randomized upon confirmation of eligibility criteria.
- Treatment Period: Week 0 (Visit 3), Week 2 (Visit 4), Week 4 (Visit 5), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (Visit 8), Week 24/EOT (Visit 9)
- Safety Follow-up: Week 28 (Visit 10)

Eligibility of subject will be confirmed as per local reading of MRI-PDFF. Baseline and Week 24/EOT MRI-PDFF assessment for Primary endpoint will be read by central laboratory. Details will be mentioned in Imaging manual. All laboratory investigations will be performed with at least 8-hours fasting blood samples. Participants will be monitored during the study at every visit for development of any AEs, including treatment emergent AEs and DILI.

10.2 STUDY PROCEDURES AT EACH VISIT

10.2.1 Screening Period

Visit 1: Screening: screening data collection (may occur over more than 1 calendar day) (-8 Weeks [-56 Days])

Before signing the consent, study procedures and all possible risks will be explained to the potential participant. After providing the written informed consent, the following study procedures will be performed:

- Check inclusion/exclusion criteria.
- Demographics (age, gender, race, ethnicity).
- Medical history.
- Concomitant medication.
- Hip circumference and minimum waist circumference.

- Weight, height, BMI, and vital signs measurement.
- Complete physical examination.
- Serum pregnancy test for all female participants of childbearing potential
- Fasting laboratory evaluations
- Biospecimen banking (plasma, serum).
- Optional biospecimen banking if consent given: stool specimen for microbiome assessment.
- FibroScan®/VCTE for LSM and CAP
- MRI-PDFF
- AUDIT alcohol history
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Serology tests (HAV IgM, HBsAg and HCV RNA)
- Urinalysis.
- AE assessments.

Visit 2: Screening: [-6 Weeks (-42 Days), +1 Week]

- Confirm inclusion/exclusion criteria
- Weight and BMI
- Targeted physical examination
- Vital signs measurement.
- Concomitant medication
- Fasting laboratory evaluations
- Urine Pregnancy test for all female participants of childbearing potential
- AE assessments.

10.2.2 Visit 3: Randomization Visit: [0 Week. Day 1, +3 days)

- Check inclusion/exclusion criteria
- Concomitant medication.
- Weight, BMI, and vital signs measurement.
- Hip circumference and minimum waist circumference.
- Targeted physical examination.
- AUDIT alcohol history
- Fasting laboratory evaluations
- Biospecimen banking (plasma, serum)
- AE assessments.
- Urine pregnancy test for all female participants of child-bearing potential.
- Randomize, administer, and dispense study medication.
- SF-36 questionnaire (Refer Appendix 4)

- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).

10.2.3 Treatment and Follow-up Period: Week 2 to Week 28

Participants will return for follow-up visits at Weeks 2, 4, 8, 12, 16, 24 and 28 after randomization. The window period of all the visits are as mentioned in Section 2 Schedule of Assessments. The specific study procedures will be performed at each follow-up visit as described below:

Visit 4: Week 2 visit (Day 15 ± 3 days)

- Concomitant medication
- AUDIT alcohol history (Refer Appendix 5 for AUDIT Questionnaire)
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Weight and BMI.
- Vital signs measurement.
- Study medication administration and compliance monitoring.
- Targeted physical examination.
- Fasting laboratory evaluations
- Urine pregnancy test for all female participants of child bearing potential.
- AE assessments.

Visit 5: Week 4 visit (Day 29 ± 3 days)

- Concomitant medication
- AUDIT alcohol history (Refer Appendix 5 for AUDIT Questionnaire)
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Weight and BMI.
- Vital signs measurement.
- Study medication administration and compliance monitoring
- Targeted physical examination.
- Fasting laboratory evaluations
- Biospecimen banking (plasma, serum).
- Urine pregnancy test for all female participants of child bearing potential.
- AE assessments.

Visit 6: Week 8 visit (Day 58 ± 3days

- Concomitant medication

- AUDIT alcohol history (Refer Appendix 5 for AUDIT Questionnaire).
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Weight and BMI.
- Vital signs measurement.
- Study medication administration and compliance monitoring
- Targeted physical examination.
- Fasting Laboratory evaluations
- Urine pregnancy test for all female participants of child bearing potential.
- AE assessments.

Visit 7: Week 12 visit (Day 85 ± 3 days)

- Concomitant medication
- AUDIT alcohol history (Refer Appendix 5 for AUDIT Questionnaire)
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Weight, BMI, hip circumference and minimum waist circumference.
- Vital signs measurement.
- Study medication administration, dispensing, and compliance monitoring
- Targeted physical examination.
- Fasting Laboratory evaluations
- Biospecimen banking (plasma, serum).
- FibroScan®/VCTE
- SF-36 questionnaire (Refer Appendix 4)
- Urine pregnancy test for all female participants of child bearing potential.
- Urinalysis.
- AE assessments.

Visit 8: Week 16 visit (Day 113 ± 3 days)

- Concomitant medication
- AUDIT alcohol history (Refer Appendix 5 for AUDIT Questionnaire).
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Weight, BMI.
- Vital signs measurement.
- Study medication administration and compliance monitoring.
- Targeted physical examination.
- Fasting Laboratory evaluations
- Urine pregnancy test for all female participants of child bearing potential.

- AE assessments.

Visit 9: Week 24/EOT visit (Day 169 ± 3 days)

- Concomitant medication
- AUDIT alcohol history (Refer Appendix 5 for AUDIT Questionnaire).
- Weight, BMI, hip circumference and minimum waist circumference.
- Vital signs measurement.
- Study medication administration and compliance monitoring
- Complete physical examination.
- Fasting Laboratory evaluations
- Biospecimen banking (plasma, serum)
- Optional biospecimen banking if consent given: stool specimen for microbiome assessment
- FibroScan®/VCTE
- MRI-PDFF
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- SF-36 questionnaire (Refer Appendix 4).
- Serum pregnancy test for all female participants of child bearing potential.
- Urinalysis.
- AE assessments.

10.2.4 Safety Follow-up Period: Visit 10: Week 28 visit (Day 197 ± 3 days)

Following assessment will be performed at the end of study visit (Week 28):

- Urine pregnancy test for all female participants of child bearing potential.
- Vital signs measurement.
- Targeted physical examination
- Weight and BMI
- Fasting Laboratory evaluations
- Concomitant medication
- AE assessment.
- Biospecimen banking (plasma)
- Study completion

10.2.5 Early Termination (ET) visit

Participants prematurely discontinued from the study would be encouraged to complete an ET visit within 30 days of last dose. The investigator should make every effort to perform following assessments at the early termination visit in case if any participant discontinues from

the study prior to completion of his/her study treatment period (i.e. termination prior to Week 24 visit):

- Complete physical examination
- Vital signs measurement.
- AE assessment.
- Concomitant medication review
- Monitoring of diet, exercise, avoidance of alcohol, and other hepatotoxic agents (Refer Appendix 8).
- Compliance review for study medication
- Weight, Hip and waist minimal circumference measurements
- Fasting Laboratory evaluations
- Serum pregnancy test for all female participants of child bearing potential.

10.3 STANDARDIZED QUESTIONNAIRES

Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire with a simple scoring scale. The purpose of the questionnaire is to ascertain whether there is significant alcohol consumption prior to enrollment or after randomization. (Appendix 5).

36-Item Short Form Health Survey (SF-36) is an easily administered questionnaire that will be used to patient-reported health-related quality of life. (Appendix 4).

10.4 ADHERENCE TO PROTOCOL

The investigator and the site staff shall strictly adhere to the protocol and International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All participants will be encouraged to strictly follow the instructions given to them as per this protocol. For any deviation or violation from protocol considered serious, the participant may be withdrawn from the study at the discretion of the sponsor or the investigator.

10.5 DATA AND SAFETY MONITORING BOARD

External oversight for this trial will be provided by an unblinded DSMB. An unblinded DSMB may meet regularly as per the DSMB charter to review interim data. The primary responsibility of the DSMB is to protect the safety and welfare of the participants participating in this clinical trial and to ensure the integrity of the clinical trial.

Specifically, for this study, the DSMB will be responsible for:

- Examining accumulated safety data and compliance data in order to make recommendations concerning continuation, termination, or modification of the trial based on the safety of the interventions under study.

- Reviewing major trial design modifications proposed by Sponsor or the investigator(s) prior to implementation of those modifications.
- The DSMB may review the safety data at any time as warranted by emerging results. Based on review of the safety data, the DSMB can recommend continuation of the study unchanged, study interruption, study termination, modification of the trial, or alteration in the DSMB monitoring plan.

Further information regarding the DSMB review process will be provided in the DSMB charter.

10.6 PROTOCOL DEVIATIONS

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.

11. STATISTICAL CONSIDERATIONS

11.1 GENERAL CONSIDERATIONS

A separate Statistical Analysis Plan (SAP) will be prepared and finalized before database lock. SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed and summary tables will be provided. Summary statistics will be presented by treatment group. Continuous variables will be summarized for the measured values and change from baseline values using the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized with counts and percent for each category.

11.2 PARTICIPANT EVALUABILITY

Assignment to all analysis populations, including decisions made on inclusion/exclusion for the per-protocol population and other data handling issues will be agreed on and documented in a blinded data review meeting, to occur (with report finalized) prior to breaking the blinded treatment assignment code and locking the database. Protocol deviations and their impact on analysis populations will be listed for all randomized participants.

11.3 ANALYSIS POPULATIONS

The following analysis populations are defined:

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

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

Intent-to-treat (ITT) Population: includes all participants who are randomized and receive at least one dose of the study drug (full or partial). Participants in the ITT population will be analyzed according to the treatment group they are assigned at randomization. The ITT population will be the primary analysis population for all efficacy analyses.

Per-Protocol (PP) Population: includes all participants in the ITT population, received at least one dose of study drug, who are compliant with the study protocol with no major protocol deviations that are expected to affect the assessment of efficacy at Week 24/EOT.

Classification of protocol deviations as major or minor will be assessed at the Blinded Data Review Meeting prior to database lock.

11.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized for ITT, PP and safety populations. All summaries will be presented by treatment group and overall.

The demographic parameters include age, gender, ethnicity and race. The baseline parameters include weight, BMI, fibrosis stage, ELF, FIB-4, APRI, NFS, PRO-C3 levels, liver stiffness, CAP, FAST score, liver parameters (ALT and AST), lipid profile parameters (Triglycerides, total cholesterol, HDL-C, LDL-C, small-dense LDL, non-HDL-C, VLDL-C), and comorbidities (Dyslipidemia, hypertension and type 2 diabetes).

11.5 PRIMARY EFFICACY ANALYSIS

11.5.1 Intercurrent Events

The following intercurrent events (ICEs) are envisioned during the study:

- Death
- Premature discontinuation of study treatment for reason other than AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention.
- Premature discontinuation of study treatment for reason of AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention.
- Receipt of prohibited medication at any point prior to Week 24 assessment.

11.5.2 Estimands for the Primary Efficacy Endpoint

Primary and secondary estimands for the primary efficacy objective "To evaluate the effect of Saroglitazar Magnesium 4 mg compared with Placebo on changes in hepatic fat content measured by MRI MRI-PDFF at Week 24/EOT." are defined below:

11.5.2.1 Definitions Applied to All Estimands

Criterion	Description
Treatment conditions of interest	Saroglitazar Magnesium 4 mg vs placebo
Population	Participants with NAFLD in PLWH

Criterion	Description
Endpoint	Change from baseline in hepatic fat content at week 24/EOT
Population level summary	Difference between treatments in change from baseline in hepatic fat content at week 24/EOT

11.5.2.2 Definitions Corresponding to Each Estimand

	Primary Estimand	Secondary Estimand
ICEs and strategies to handle ICEs	• Death prior to assessment at Week 24 *Composite strategy* • Premature discontinuation of study treatment for reason of AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention *Treatment policy strategy* • Premature discontinuation of study treatment for reason other than AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention *Treatment policy strategy* • Receipt of prohibited medication at any point up to Week 24 *Treatment policy strategy*	• Death prior to assessment at Week 24 *Composite strategy* • Premature discontinuation of study treatment for reason of AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention *Hypothetical strategy* • Premature discontinuation of study treatment for reason other than AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention *Hypothetical strategy* • Receipt of prohibited medication at any point up to Week 24 *Hypothetical strategy*
	ICE(s) with a composite variable strategy take priority over ICEs with other strategies.	

Where the strategies are described as follows in the sequence these strategies will be applied:

- <u>For the primary estimand:</u>
  - *Composite strategy:* missing data will be handled by imputing using the worst outcome of MRI-PDFF across either treatment arm.
    - *Treatment policy strategy:* available data occurring on or after the ICE will be analyzed as observed. Any missing Week 24 MRI-PDFF data due to discontinuation of study treatment for reason other than AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention will be multiple imputed using a missing at random (MAR) approach.
  - <u>For the secondary estimand:</u>
  - *Composite variable strategy:* missing data will be handled by imputing using the worst outcome of MRI PDFF across either treatment arm.

- *Hypothetical strategy:* the approach allows for the assessment of the treatment effect in an alternative, hypothetical setting where 1) all participants take the assigned study treatment without discontinuation/interruption, and 2) prohibited medication was not available to participants for the study duration. Available data occurring on or after the ICE will be set to missing, and multiple imputed by a MNAR application of SAS Proc MI based on the distribution of data for each treatment arm where all participants do not experience an ICE.

11.5.3 Statistical Hypotheses

- The superiority hypotheses for comparing Saroglitazar Magnesium 4 mg to Placebo are
  - H_0: $\mu_p - \mu_s \leq 0$
  - H_1: $\mu_p - \mu_s > 0$
- Where μ_s is the change from baseline to Week 24 in liver fat content for Saroglitazar 4 mg arm and μ_p is the change from baseline to Week 24 in liver fat content for placebo arm.

11.5.4 Statistical Methods

Comparison of change from baseline in hepatic fat content between Saroglitazar 4 mg and placebo will be evaluated using mixed models for repeated measures (MMRM) including visit and treatment as factors, baseline value as a covariate and an interaction term treatment x visit. The p-value for the treatment differences (Saroglitazar Magnesium versus Placebo), estimate of LSMEANS treatment difference (Saroglitazar Magnesium – Placebo), and the two-sided 90% confidence interval of the LSMEANS difference will be generated from the MMRM model. Observed values and changes from baseline will be summarized descriptively at each visit for all continuous parameters. The primary endpoint will be analyzed based on the ITT population.

11.5.5 Subgroups

The following subgroup populations will be investigated for the main estimand using ITT population:

- Age category (< 65 years and ≥ 65 years)
- Gender (male and female).
- Race
- Ethnicity
- Baseline Type 2 Diabetes.

11.5.6 Handling of Missing Data

Every effort will be made to prevent participants early terminating the study and for participants who discontinue study drug, every effort will be made to continue to collect data after

discontinuation. Where missing data exist for primary and secondary efficacy endpoints, imputation will occur where specified.

The primary method of imputation for missing data will be MI (Multiple Imputation); the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, as the biopsy will be performed only at screening and at Week 24/EOT visits.

A logistic regression model will be used for the ordinal scores and linear regression will be used for the continuous variable.

The imputed datasets will be analyzed using the methodology described in Section 11.5. The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS system. The number of imputations and the seed to be used, plus any further details required, will be detailed in the SAP.

11.5.7 Sensitivity and Supportive Analyses

The following sensitivity and supportive measures will be conducted for the primary efficacy endpoint:

Estimand	Analysis Set	Modelling and Data Handling Method
Primary and secondary	PPS	Same as primary analysis method. Repeat on primary and secondary estimands with same imputation approach for missing data.

11.6 SECONDARY EFFICACY ENDPOINT AND ANALYSIS

11.6.1 Definitions Applying to All Estimands

Criterion	Description
Treatment conditions of interest	Saroglitazar Magnesium 4mg vs placebo
Population	Participants with NAFLD in PLWH

11.6.2 Details of Each Estimand for the Secondary Efficacy Endpoints Involved in Construction of the Primary Efficacy Endpoint

Endpoint	Population Level Summary	Primary Estimand	Secondary Estimand
Reduction of at least 30% in hepatic fat content from baseline following 24 weeks/EOT	Difference between treatments in proportion of participants with reduction of at least 30% in hepatic fat content from baseline following 24 weeks/EOT	Same as primary efficacy endpoint	Same as primary efficacy endpoint

11.6.3 Details of Each Estimand for the Secondary Efficacy Endpoints Not Involved in Construction of the Primary Efficacy Endpoint

Endpoint	Population Level Summary	Primary Estimand	Secondary Estimand
LSM, CAP and FAST scores measured by FibroScan®/VCTE	Difference between treatments in mean change from baseline in LSM, CAP and FAST scores at Week 24/EOT.	• Death prior to assessment at Week 24 *Composite strategy* • Premature discontinuation of study treatment for reason other than AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention *Treatment policy strategy* • Premature discontinuation of study treatment for reason of AE, lack of efficacy (LoE), liver transplant, hepatic decompensation or bariatric intervention *Treatment policy strategy* • Receipt of prohibited medication at any point up to Week 24 *Treatment policy strategy*	Not applicable
Non-invasive markers of fibrosis and steatosis (PRO-C3, FIB-4, APRI, NFS)	Difference between treatments in mean change from baseline in non-invasive markers of fibrosis and steatosis (PRO-C3, FIB-4, APRI, NFS) at Week 24/EOT.		
Liver enzyme parameters (ALT and AST), Lipid parameters (TG, HDL, LDL, VLDL, TC, non-HDL) and insulin resistance and glucose homeostasis markers (HbA1c, FPG)	Difference between treatments in mean change from baseline in liver enzyme parameters (ALT and AST), lipid parameters (TG, HDL, LDL, VLDL, TC, non-HDL) and insulin resistance and glucose homeostasis markers (HbA1c, FPG) at Week 24/EOT.		
Body weight, BMI, hip circumference and minimum waist circumference	Difference between treatments in mean change from baseline in body weight, BMI, hip circumference and minimum waist circumference at Week 24/EOT.		

Endpoint	Population Level Summary	Primary Estimand	Secondary Estimand
Health related quality of life score measured by SF-36 Questionnaire	Difference between treatments in mean change from baseline in SF-36 Questionnaire mental (MCS) and physical components scores (PCS) at Week 24/EOT.		

Where the strategies are described as follows in the sequence these strategies will be applied:

- For the primary estimand:

Composite strategy: Death prior to Week 24 assessment will be handled by imputing using the worst outcome observed for the parameter across either treatment arm.

Treatment policy strategy: available data occurring on or after the ICE will be analyzed as observed. Any missing Week 24 data for the corresponding assessment will not be imputed.

For secondary efficacy endpoints not related to construction of the primary efficacy endpoint, only the primary estimand will be assessed.

11.6.4 Statistical Methods for the Analysis of Secondary Efficacy Endpoints.

The high-level handling approaches for the secondary efficacy endpoints are as follows:

Endpoint	Analysis Set	Modelling Method	Data Handling
Primary Efficacy Endpoints			
Change from baseline in hepatic fat content at week 24/EOT	ITT, PPS	Mixed-effect repeated measures model (MMRM)	As per primary and secondary estimands for the primary efficacy endpoint.
Other Secondary Efficacy Endpoints			
Proportion of participants with reduction of at least 30% in hepatic fat content from baseline following 24 weeks/EOT	ITT, PPS	Chi-square test as per primary efficacy endpoint analysis.	As per primary and secondary estimands for the primary efficacy endpoint.
Change from baseline in Liver Stiffness Measurement (LSM), Continuous Controlled Attenuation Parameter (CAP), and FibroScan -AST (FAST) score at Week 24/EOT.	ITT	Mixed-effect repeated measures model (MMRM)	As per primary estimand for secondary efficacy endpoints. Missing data will not be imputed.
Change from baseline in non-invasive markers of fibrosis and steatosis (PRO-C3 levels, FIB-4, APRI and NFS) at Week 24/EOT.	ITT	MMRM	As per primary estimand for secondary efficacy endpoints. Missing data will not be imputed.

Endpoint	Analysis Set	Modelling Method	Data Handling
Change from baseline in liver enzyme parameters (ALT and AST) at Week 24/EOT and lipid parameters (TG, HDL, LDL, VLDL, TC, non-HDL) at Week 24/EOT and insulin resistance and glucose homeostasis markers (FPG and HbA1c index) at Week 24/EOT	ITT	MMRM	As per primary estimand for secondary efficacy endpoints. Missing data will not be imputed.
Change from baseline in body weight, BMI, hip circumference and minimum waist circumference at Week 24/EOT.	ITT	MMRM	As per primary estimand for secondary efficacy endpoints. Missing data will not be imputed.
Change from baseline in SF-36 Questionnaire mental (MCS) and physical components scores (PCS) at Week 24/EOT.	ITT	MMRM	As per primary estimand for secondary efficacy endpoints. Missing data will not be imputed.

11.7 MULTIPLICITY

Not Applicable

11.8 Exploratory Analyses

The exploratory efficacy analysis will be described in the Statistical Analysis Plan.

11.9 SAFETY ANALYSIS

11.9.1 Treatment Exposure

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 duration and compliance will be summarized descriptively as a continuous measure. In addition, a categorical summary of compliance will also be presented using the following categories: <80%, 80% to 120%, and >120%. A participant is considered to be compliant, if he/she takes 80% to 120% of the study drug during the study period.

11.9.2 Medical History

Relevant medical history will be tabulated by system organ class and preferred term of the MedDRA dictionary (latest version) presented by treatment group.

11.9.3 Concomitant Therapies

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.

11.9.4 Safety Parameters

The following safety parameters will be descriptively analyzed:

- Frequency and severity of treatment emergent AEs, serious AEs, and AESIs.
- Changes in vital sign parameters (Systolic BP, diastolic BP, pulse rate, temperature, and respiratory rate)
- Changes in clinical laboratory testing parameters (hematology, clinical chemistry, hormonal profile, and urinalysis)
- Changes in physical examination assessments

AESI includes DILI and weight gain, which would be closely monitored.

AEs/SAEs will be coded using the MedDRA dictionary and presented by system organ class and preferred term. Treatment emergent AEs will be analyzed based on the number and percentage of participants with at least one AE in the category of interest. Additional summaries will be provided by severity and causality. SAEs and AEs leading to discontinuation of study treatment will also be summarized separately. Participant listings of all AEs will be provided. Deaths and other serious or clinically significant non-fatal AEs will be listed separately.

Observed values and changes from baseline will be summarized for the laboratory data and vital signs. Laboratory values will be categorized as low/normal/high according to normal ranges, and shift tables versus baseline will be created to determine treatment-emergent abnormalities. DILI events, as well as important biological consideration events (per Section 7.6) will be categorized based on the relevant laboratory parameters, and summarized by treatment group.

11.10 INTERIM ANALYSIS

No interim analysis is planned for this study.

11.11 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint is the mean change from baseline in hepatic fat content assessed by MRI-PDFF at Week 24/EOT in participants with NAFLD. In a previously conducted Phase 2 study in NAFLD participants, the mean change from baseline in hepatic fat content at Week 16 in Saroglitazar 4 mg group was -4.2 (SD=6.2) and in Placebo was -0.3 (SD=5.7).

Assuming a similar treatment effect on hepatic fat content in Saroglitazar 4 mg group at Week 24/EOT in this study, a sample size of 102 participants (51 participants in each treatment arm) will provide 80% power to detect a treatment difference of at least 3 in change from baseline in hepatic fat content at Week 24 between Saroglitazar 4 mg and Placebo using a one-sided 5% level of significance based on two-sided t-test, assuming a common standard deviation of 6.

Assuming a dropout rate of 15% at week 24, approximately 120 participants (60 participants in each treatment arm) will be randomized in a 1:1 ratio to receive either Saroglitazar 4 mg or placebo.

11.12 COVID-19 CONSIDERATIONS

Given the current COVID-19 pandemic, per regulatory guidance, a listing of participants either experiencing COVID-19 infection or at least possibly affected by COVID-19 related measures will be produced where applicable. Further details relating to additional populations and subgroup analyses, handling of protocol deviations, handling of missing data (including use of virtual assessments and/or switches from local to centralized labs), and any other considerations related to COVID-19 infection and related measures will be detailed further in the SAP, finalized before unblinding.

12. ADMINISTRATIVE MATTERS

The study will be carried out in compliance with the protocol, in accordance with the ICH GCP and other applicable regulatory guidelines.

12.1 ETHICS

12.1.1 Institutional Committee Review and Communications

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent, and any accompanying material to be provided to the participant to the IRB. The trial will not be initiated before the protocol and informed consent, and any accompanying material have been reviewed and have received approval/favorable opinion from the IRB. The study will use a single IRB (sIRB) for its IRB of record. Each site and the sIRB will have a fully signed IRB Authorization Agreement (IAA) in place for the duration of the study. Should a protocol amendment be written that requires IRB approval, the changes in the protocol will not be instituted until the amendment and revised informed consent (if appropriate) has been reviewed and received approval/favorable opinion from the sIRB. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the appropriate regulatory authorities and sIRB are notified as soon as possible and an approval is requested. Protocol amendments only for logistical or administrative changes may be implemented immediately; however, both the sIRB and the Regulatory Authorities will be notified as soon as possible.

The constitution of the IRB must comply with the requirements of the US Code of Federal Regulations (CFRs) or applicable regulatory agency. A list of the IRB members, with names and qualifications, will be requested. If such a list is unavailable, the investigator or designee must provide the name and address of the IRB along with a statement from the IRB that it is organized according to GCP and the applicable laws and regulations. The IRB must also perform all duties outlined by the requirements of the regulatory agencies.

12.1.2 Informed Consent and Participant Information

Prior to participation in the study, written informed consent will be obtained from each participant (or the participant's legally accepted representative) according to the regulatory and legal requirements of the participating site. Virtual verbal consent may be allowed at certain sites per IRB approval with signatures obtained at the first screening visit. Each signature must be dated by each signatory. The informed consent and all study data forms will be retained by the investigator or designee as part of the study records. A signed copy of the informed consent and recruitment materials must be given to each participant or the participant's legally authorized representative.

A written informed consent will also be obtained from each participant for the optional banking assessments. A legally accepted representative of the participant is not permitted to consent for the optional banking assessments.

The participant must be informed that his/her medical records may be examined by authorized monitors or Clinical Quality auditors appointed by the sponsor, by appropriate IRB members and by inspectors from regulatory authorities.

Should a protocol amendment be made, the participant informed consent form and recruitment materials may need to be revised to reflect the changes to the protocol. It is the responsibility of the investigator to ensure that an amended consent form is reviewed and has received approval/favorable opinion from the IRB and that it is signed by all participants subsequently entered in the study and those currently in the study, if affected by the amendment.

12.1.3 Compensation and Insurance

Participants will not be required to pay for the study medications and laboratory investigations, if they participate in this study. If the participants develop a medical condition as a result of participation in this study, including SAEs, he/she will receive emergency care; out-patient care or hospitalization including proper referral, as needed. Zydus Therapeutics Inc. is the sponsor of the study and has an insurance cover, which will pay the medical expenses for the treatment of such conditions. This insurance covers damages or injury or death resulting from participation in a study and which are mentioned during the participation in the study. Any injury or damages or death will be reported to the insurer. Participants should report any discomforts, problems, or research related injuries immediately to study Investigator or study staff. In case of injury occurring to participants during the clinical trial as a result of taking the study drug(s) or from the procedures done for the purpose of this study, the sponsor will pay for those medical expenses necessary to treat the injury that are not covered by the participant's medical insurance or any other third-party coverage.

12.2 RECORD KEEPING

12.2.1 Drug Accountability

Drug supplies, which will be provided by the sponsor, must be kept in a secure, controlled access storage area under the storage conditions defined by the sponsor. A temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The investigator/designee and/or pharmacist must maintain records of the product's delivery to the study site, the inventory at the site, the dispensation to each participant and the return to the sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the IP(s) and study participants. The investigator or designee will maintain records, that document adequately, that the participants were provided the doses specified by the protocol and reconcile all IP(s) received from the sponsor. At the time of return to the sponsor, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the study participants and that no remaining supplies are in the investigator's or site's possession.

12.2.2 Emergency Code Break (Unblinding)

An emergency code break will be available to the Investigator and/or pharmacist. This code break must only be opened in emergency situations when the identity of the study medication must be known by the Investigator in order to provide appropriate medical treatment. If the code break for a participant is opened, Sponsor must be informed immediately. The reason for opening the code break must be documented along with the date and the initials of the person who broke the code. Participants whose treatment assignment becomes unblinded inadvertently, need not require to complete the scheduled evaluations and the participant will be withdrawn from the trial from that visit.

12.2.3 Electronic Case Report Forms

For each participant enrolled, the eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the participant visit to enable the sponsor to perform central monitoring of safety data, whenever possible. The eligibility criteria eCRF should be completed only after all data related to eligibility have been received and the participant has been enrolled.

Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator or designee will use his/her login credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol Schedule of Assessments. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or sponsor staff who routinely review the data for completeness, correctness, and consistency. The site coordinator or designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g., data entry error).

12.2.4 Data Management

12.2.4.1 Data Handling

Detailed data management plan will be prepared for this study. Data will be recorded by the investigator or designee into CRFs and reviewed by the study monitor during monitoring visits. The study monitor will verify data recorded in the EDC system against source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. A CRF will be considered complete when all missing, incorrect and/or inconsistent data has been accounted for and the CRF is signed by the investigator.

12.2.4.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.2.4.3 Data Entry

Data must be recorded in to the EDC system in a timely manner as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with the appropriate international regulations. All passwords will be strictly confidential.

12.2.4.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of Medical Dictionary for Regulatory Activities (MedDRA) for AEs and medical history
- Latest version of WHO Drug Dictionary for prior and concomitant medications.

12.2.4.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for reconciliation/resolution through data queries.

The CRFs must be reviewed and approved/signed by the investigator.

12.2.5 Source Documents

Source documents will be "all original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions

certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial)".

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data reported in the EDC must be consistent with the source CRF documents or the discrepancies must be explained.

The investigator or designee may need to request previous medical records from another institution, depending on the study; also, current medical records – not just shadow charts – must be available.

The following data to be reported on the CRF should be included and derived from participant interview or source documents but not limited to:

- Participant identification (gender, date of birth/age)
- Participant participation in the trial (medication, trial number, participant number, date informed consent given)
- Dates of participant's visits
- Medical/surgical/alcohol history
- Medication history
- AE onset and end date and time
- SAE onset and end date and time
- Originals or copies of laboratory results, VCTE/FibroScan® findings, and other results if applicable
- Conclusion of a participant's participation in the trial

12.2.6 Direct access to Source Data/Documents

The investigator/institution will permit Sponsor/Sponsor's designee for trial-related monitoring and audits, IRB review and regulatory inspection, providing direct access to all related source data/documents. Source data is defined as "All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)".

Case Report Forms and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor and inspection by the health authorities (e.g., FDA, or other applicable regulatory authorities). The monitor will review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in the Section 12.2.4.

12.2.7 Trial Monitoring

It is the responsibility of the investigator to ensure that the study is conducted in accordance with the protocol, US CFR applicable to clinical trials 45 CFR Part 46, and applicable regulatory requirements and that valid data are entered into the CRFs.

To achieve this objective, the study monitor's duties are to aid the investigator, and, at the same time, the sponsor in the maintenance of complete, legible, well-organized and easily retrievable data. Before the enrollment of any participant in this study, the sponsor or their designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs, and procedures for their completion, informed consent process and the procedure for reporting SAEs.

The investigator will permit the sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the monitor will review the data (through onsite monitoring visits and/or remote monitoring) for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

12.3 QUALITY AUDITS

Quality audits of this study may be conducted by the sponsor or sponsor's designees. The quality auditor must have access to all medical records, the study-related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

12.4 PROCEDURES

12.4.1 Adverse Events

Adverse event reporting will begin after the informed consent has been signed and will continue until end of the study (i.e., the safety follow-up). The National Cancer Institute's CTCAE (Version 5.0 or higher) will be used for reporting and grading AEs when possible.

12.4.1.1 Definitions

An AE is any unfavorable or unintended sign, symptom or disease temporally associated with the use of the study medication whether or not considered related to the study medication (21 CFR 312.32 [a]).

Adverse events may include:

- Objective signs observed by the investigator or the study personnel
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a participant in the course of a clinical study
- Pre-existing conditions that worsen in severity or frequency or have new signs/symptoms associated with them

Findings related to abnormal laboratory values and vital signs, which are not considered clinically significant, are not to be recorded on the AE reporting page; such events should instead be entered in the relevant CRF page.

12.4.1.2 Treatment-emergent Adverse Events

Treatment-emergent AEs are defined as any AE that started after the first dose of the study medication or started before the first dose but increased in severity or frequency after administration of the initial dose of the study medication.

12.4.1.3 Collection of Adverse Events

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings, e.g., "How have you felt since I saw you last?" AEs will be recorded on study data forms whether or not they are thought to be associated with the study or with the study drug. AEs may be discovered during regularly scheduled visits or through unscheduled patient contacts between visits.

12.4.1.4 Assessment of Adverse Events

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity. Each AE will be assessed by the investigator with regard to the following categories:

Severity

The investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the participant's CRF.

Severity will be assessed according to the following scale:

- **Mild**: Event is usually transient and easily tolerated, requiring no special treatment and causing no disruption of the participant's normal daily activities
- **Moderate**: Event introduces a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually improved by simple therapeutic measures. Moderate experiences may cause some interference with functioning.
- **Severe**: Event interrupts the participant's normal daily activities and generally requires systemic drug therapy or other treatment. Severe events are usually incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- **Fatal**

Causality

For all AEs, the investigator will provide an assessment of causal relationship to the study medication. The causality assessment must be recorded on the appropriate AE reporting page of the participant's CRF.

Causal relationship will be classified according to the following criteria:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.
- **Unknown**

Outcome

Outcome of AEs will be defined according to the ICH topic E2B, ICH Guideline, as follows:

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Not Recovered/Not Resolved
- Fatal
- Unknown

12.4.1.5 Recording Adverse Events

All AEs must be recorded on the appropriate AE CRF for the participant. All AEs must be reported whether or not considered causally related to the study medication. For every AE, the investigator will provide an assessment of the severity and causal relationship to the study medication, will document all actions taken with regard to the study medication, and will document any other treatment measures for the AE. If an outcome for an AE is not available at the time of the initial report, follow-up will proceed until an outcome is known.

12.4.1.6 Follow-up of Adverse Events

All AEs experienced by a participant, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the participant is lost to follow-up or the participant has died.

12.4.2 Serious Adverse Event

An SAE is an event that:

- Results in death
- Is life threatening
- Results in persistent or significant disability/incapacity
- Results in inpatient hospitalization or prolongs an existing inpatient hospitalization
- Is a congenital anomaly/birth defect
- Is another important medical event that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above

Serious AEs also include events that are medically significant in the investigator's judgment, including medically significant laboratory abnormalities, such as those that warrant stopping the study medication for individual participants, as specified in the Section 7.6 of the protocol. In general, medically significant events require medical/surgical intervention to prevent one of the outcomes listed above.

12.4.2.1 Reporting Serious Adverse Events

The investigator must report any SAEs to the Sponsor/Service provider within 24 hours of becoming aware of the event.

During SAE reporting, the reporting SAE, the investigator's name, participants name and the telephone number with the protocol number and title will be recorded. Details regarding the safety management will be specified in safety management plan.

The investigator and the sponsor (or sponsor's designated personnel) will review each SAE report and the sponsor will evaluate the seriousness and the causal relationship of the event to the study medication. In addition, the sponsor (or sponsor's designated personnel) will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics).

Based on the investigator and sponsor's assessment of the event, a decision will be made concerning the need for further action. All SAEs will be recorded from first dose of study medication until the end of the study (i.e., the safety follow-up). Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours.

The study sponsor or designee will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for

reporting. If the FDA determines that a change to the investigator's brochure, IND, or protocol is needed, the Sponsor will send a copy of the IND Safety Report to the IRB, and all clinical centers, with instructions to forward the report to their local IRB.

12.4.3 Hepatic Safety Adjudication Committee

A separate blinded HSAC will be established. The committee will review, monitor and adjudicate possible cases of DILI in the study.

Participants will be categorized as those for whom DILI or worsening of hepatic function attributable to study drug could be excluded (e.g., a clear, alternative explanation exists); those for whom DILI or worsening of hepatic function attributable to study drug could not be excluded (e.g., no clear, alternative explanation exists); and those with insufficient data to make a determination. Potential cases of DILI will be adjudicated during the treatment period.

Further information regarding the HSAC review process will be provided in the HSAC charter.

12.4.4 Expected Adverse Events

No Suspected Adverse Reactions are considered expected by the sponsor for the purpose of expedited reporting of Suspected Unexpected Serious Adverse Reactions. .

12.4.5 Pregnancy

From screening to end of study, every female participant will be investigated for child-bearing potential and need for urine pregnancy test. Participants shall be advised to not become pregnant during the trial and for at least one month after the end of the trial period. Adequate contraceptive measures should be taken to prevent pregnancy. Refer Appendix 3: Contraceptive Guidance. Even when contraceptive methods are used, there is a small risk that pregnancy might occur. In case a female participant becomes pregnant, the study medication will be stopped immediately. The participant will be withdrawn from the study drug and adequate monitoring of the participant will be performed.

Women who become pregnant while on trial drug (and up to 4 weeks ± 3 days following active treatment), an adequate monitoring will be done as follows:

a. If the woman wants to continue the pregnancy, she will be provided proper obstetrical care.

b. The investigator should ensure that the participant has access to an obstetrician for the entire duration of her pregnancy and the delivery. The investigator should regularly follow up with the obstetrician regarding the health status of the participant. If the woman decides to terminate her

pregnancy, she will be provided proper gynecological care. The investigator should ensure that the participant has access to a gynecologist for the termination of her pregnancy. The investigator should regularly follow up with the gynecologist regarding the health status of the participant.

Although pregnancy and lactation are not considered AEs, it is the responsibility of the investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the trial to the Sponsor, IRB, and DMC within 3 business days and unblinding may be considered depending on the DMC's input. All female participants who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the sponsor as mentioned in the Section 12.4.2.1.Pregnancies that occur on study medication should be reported prospectively to The Antiretroviral Pregnancy Registry by the investigators. More information is available at www.apregistry.com.

Address
The Antiretroviral Pregnancy Registry
301 Government Center Drive
Wilmington, NC 28403
US, Canada (toll-free): Phone: 800-258-4263
Fax: 800-800-1052
E-Mail: SM_APR@APRegistry.com

12.5 UNANTICIPATED PROBLEMS

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.6 RULES FOR AMENDING PROTOCOL

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB, in accordance with local legal and regulatory requirements. This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive the IRB approval before implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted. Refer Appendix 10

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

12.7 FINANCIAL DISCLOSURE

The investigators are required to provide financial disclosure information to the sponsor to permit the sponsor to fulfil its obligations. In addition, the investigators must commit to promptly update this information if any relevant changes occur during the study and for a period of one year after the completion of the study.

12.8 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The sponsor reserves the right to discontinue this study at any time for failure to meet expected enrollment goals, for safety, or any administrative reasons. The investigator will be reimbursed for reasonable expenses incurred if it is necessary to terminate the study as per the agreement.

12.9 STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions of participating physicians, and site personnel, the sponsor's representatives, monitor, auditor, to the IRB and the regulatory health authorities as required under the law. Participant confidentiality will be further ensured by utilizing participant identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this study are to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB and the regulatory health authorities.

12.10 FINAL REPORT AND PUBLICATION POLICY

The Final Study Report will include the tabulated raw data, the biostatistical analysis, and interpretation of the study results. By signing the clinical study protocol, the investigator agrees with the use of the study results for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the relevant authorities will be notified of the investigator's name, address, qualifications and extent of involvement. An investigator shall not publish any data (poster, abstract, paper, etc.) without prior written permission of the sponsor.

12.11 ARCHIVING

Participant's files, identification codes and other source data (including original reports of test results, dispensing logs, records of informed consent), IRB approval letter, correspondence and other documents pertaining to the conduct of the study will be kept as per the SOPs of the institution. According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug. However, these documents should be retained for a longer period if required by the applicable legal requirements. No document pertinent to the study shall be destroyed without prior written agreement between the sponsor and the investigator.

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14. SIGNATURE PAGE(S)

SPONSOR APPROVAL

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.

I have read, understood and approve this protocol.

I agree to comply with all requirements regarding the obligations of Sponsor and all other pertinent requirements of Declaration of Helsinki (Fortaleza, 2013) and ICH E6 the guidelines on Good Clinical Practice (GCP) and any other applicable regulatory requirements.

_____ **Date: _____**

AUTHORIZED SIGNATORY

[redacted]

APPROVAL FROM PROTOCOL CO-CHAIR

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.

I have read, understood and approve this protocol.

[redacted]

[redacted]

DECLARATION OF THE LEAD PRINCIPAL INVESTIGATOR

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.

I, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of Principal Investigator(s) and all other pertinent requirements of the ICH E6 'Guidelines on Good Clinical Practice', Declaration of Helsinki (Fortaleza, 2013) and applicable regulatory authorities.

All documentation for this study that is supplied to me, and that has not been previously published, will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, Case Report Forms and other scientific data. Copying, disclosing and publishing without written consent of Sponsor is prohibited.

The study will not be commenced without the prior written approval of Regulatory Authorities and a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to eliminate an immediate hazard to the patients.

I further agree to ensure that all associates assisting in the conduct of this study are well informed regarding their obligations and confirm to conduct this study under my direction at the following address:

[redacted]

_____

Signature and Date

Note: Please retain original page of the Investigator's declaration at the site and send a copy of this page to the Sponsor.

DECLARATION OF PRINCIPAL INVESTIGATOR

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.

I, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with this protocol and to comply with all requirements regarding the obligations of Principal Investigator(s) and all other pertinent requirements of the ICH E6 'Guidelines on Good Clinical Practice', Declaration of Helsinki (Fortaleza, 2013) and applicable regulatory authorities.

All documentation for this study that is supplied to me, and that has not been previously published, will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, Case Report Forms and other scientific data. Copying, disclosing and publishing without written consent of Sponsor is prohibited.

The study will not be commenced without the prior written approval of Regulatory Authorities and a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB, except where necessary to eliminate an immediate hazard to the patients.

I further agree to ensure that all associates assisting in the conduct of this study are well informed regarding their obligations and confirm to conduct this study under my direction at the following address:

Name of the Principal Investigator:

Name and Address of the site:

_____

Signature and Date

Note: Please retain original page of the Investigator's declaration at the site and send a copy of this page to the Sponsor.

15. APPENDICES

15.1 APPENDIX 1: PARTICIPATING STUDY CENTERS

Study Centers	[redacted]

15.2 APPENDIX 2: LIST OF KNOWN CYP2C8 INHIBITORS/SUBSTRATES

Selected inducers, inhibitors and substrates of CYP2C8

Substrates	Inhibitors	Inducers
a. Amodiaquine[a] (antimalarial, anti-inflammatory) b. Cerivastatin[a] (statin) c. Enzalutamide (antiandrogen) d. Paclitaxel[a](chemotherapeutic) e. Repaglinide[a] (antidiabetic) f. Torsemide[a] (loop diuretic) g. Sorafenib[a] (tyrosine kinase inhibitor) h. Rosiglitazone (antidiabetic) - converted to active metabolites[b] i. Buprenorphine (semisynthetic opioid) j. Montelukast (leukotriene receptor antagonist)	**Strong** a. Gemfibrozil[a](Hypolipidemic) **Moderate** a. Trimethoprim[a](Antibiotic) **Unspecified potency** a. Thiazolidinediones[a](antidiabetic) b. Montelukast[a](leukotriene receptor antagonist) c. Quercetin[a](anti-inflammatory)	**Unspecified potency** a. Rifampicin[a](Antibiotic)

[a] Flockhart DA (2007). "Drug Interactions: Cytochrome P450 Drug Interaction Table". Indiana University School of Medicine. Retrieved on July 2011

[b] Chapter 26 in: Rod Flower; Humphrey P. Rang; Maureen M. Dale; Ritter, James M. (2007). Rang & Dale's pharmacology. Edinburgh: Churchill Livingstone. ISBN 0-443-06911-5

15.3 APPENDIX 3: CONTRACEPTIVE GUIDANCE

In order to include women of childbearing potential (WOCBP) in any clinical study, certain precautions pertaining to pregnancy must be taken. These will include pregnancy urine and serum testing at screening and visits as defined in the protocol (Section 2 Schedule of Assessments) and as per local regulations. Pregnancy should be avoided by either complete abstinence or the use of an acceptable effective contraceptive measures for the duration of the study and for at least 1 month after the end of the study treatment.

Female participants who become pregnant during a study will be withdrawn and adequately monitored until the outcome of the pregnancy.

Definitions:

•WOCBP: A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

•A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Contraception Guidance:

•Male Participants:

Male participants with female partners of childbearing potential should agree to use one of the following:

1.Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent for duration of study.

2.Agree to use condom or have their partner use of a contraceptive method as described below when having penile-vaginal intercourse with WOCBP who are not currently pregnant.

Female participants: Female participants of childbearing potential should agree to use an acceptable effective method of contraception consistently and correctly for the duration of the study and for at least 1 month after the end of the study treatment.as described below

Highly Effective Contraceptive Methods (having a failure rate of less than 1% per year)

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Oral. Intravaginal. Transdermal.
Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral. Injectable. Implantable.
Implantable progestogen only hormonal contraception associated with inhibition of ovulation Intrauterine device. Intrauterine hormone-releasing system. Bilateral tubal occlusion.
Vasectomized partner A vasectomized partner is a highly effective birth control method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Acceptable Birth Control Methods (having a failure rate of more than 1% per year)

- Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Spermicides alone are inefficient at preventing pregnancy. Therefore, spermicides alone are not an acceptable method of contraception.

Pregnancy Testing:

Any WOCBP should only be included after a confirmed menstrual period and a negative serum and urine pregnancy test as defined in the protocol. Additional pregnancy testing will be done as specified in the protocol during the treatment period and as per local regulations (if any).

Pregnancy testing will also be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

15.4 APPENDIX 3: HEALTH-RELATED QUALITY OF LIFE ASSESSMENT QUESTIONNAIRE

https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html

15.5 APPENDIX 4: AUDIT QUESTIONNAIRE

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems.

A self-report version of the AUDIT is provided. Patients should be encouraged to answer the AUDIT questions in terms of standard drinks. A chart illustrating the approximate number of standard drinks in different alcohol beverages is included for reference in the link below. A score of 8 or more is considered to indicate hazardous or harmful alcohol use. The AUDIT has been validated across genders and in a wide range of racial/ethnic groups and is well suited for use in primary care settings.

Detailed guidelines about use of the AUDIT have been published by the WHO and are available online in the link below:

https://www.drugabuse.gov/sites/default/files/audit.pdf

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

15.6 APPENDIX 6: CKD-EPI CALCULATOR

This CKD-EPI equation calculator should be used when S_{cr} is reported in µmol/L. This equation is recommended when eGFR values above 60 mL/min/1.73 m² are desired.

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if African American]

where:
S_{cr} is serum creatinine in µmol/L,
κ is 61.9 for females and 79.6 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1
The equation does not require weight because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area.

Please refer: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units

15.7 APPENDIX 7: LIST OF STEATOGENIC MEDICATIONS OR SUPRA-PHYSIOLOGIC HORMONAL THERAPIES OR MEDICATIONS THAT CAUSE SIGNIFICANT WEIGHT CHANGE

Steatogenic Medications	1. Amiodarone 2. Tamoxifen 3. Methotrexate 4. Systemic glucocorticoids 5. Anabolic steroids 6. Tetracycline 7. Vitamin A 8. L-asparaginase 9. Valproate 10. Chloroquine 11. Stavudine
Supra-Physiologic Hormonal Therapies	1. Estrogen in doses higher than used in oral contraceptives or post-menopausal hormone replacement therapy (except for transgender women on stable dosing)
Medications that can cause significant weight change	1. Phentermine 2. Topiramate 3. Orlistat 4. Bupropion 5. Naltrexone

15.8 APPENDIX 8: DIET AND EXERCISE GUIDANCE

1. DIETARY INTAKE:

a. Patients without diabetes will be instructed to follow the National Cholesterol Education Program (NCEP) Step 1 recommendations (Refer Table 1 of this appendix). These recommendations will include specific discussions on total caloric intake, the amount and type of fat consumed, and the amount of carbohydrate consumed.
b. The importance of portion control will be discussed, especially in reference to eating at restaurants. Avoidance of calorie dense fast food and sugar sweetened beverages will be stressed.
c. Patients with known or newly discovered type 2 diabetes will receive specific recommendations as promulgated by the American Diabetes Association (ADA) (Refer Table 2 of this appendix).
d. Recommendations regarding the use of specific nutritional supplements are addressed below.
e. Dietary guidelines may not apply to all participants or situations.

2. WEIGHT LOSS

a. Overweight participants (BMI >25 kg/m^2) will be given a goal of losing and sustaining the loss of 5%-10% of body weight. This weight loss should be achieved at a rate of 1-2 lbs per week per NHLBI guidelines (Refer Table 3 of this appendix).
b. Patients will be instructed not to fast as a means of achieving weight loss.
c. Alternative diet plans intended to promote weight loss will be considered individually based on nutritional completeness.

3. ALCOHOL CONSUMPTION

Patients will be instructed that total abstinence from alcohol is advisable. The Committee acknowledges the paucity of data regarding a minimal safe dose of alcohol in individuals with liver disease and consumption limited to “ceremonial use” or even amounts up to 10 g per week (1 oz 80 proof liquor, 3.5 oz non-fortified wine, 8 oz beer) may be safe.

4. EXERCISE

Patients will be instructed to engage in a lifestyle that includes regular moderate exercise. The recommendations of the Institute of Medicine will be used: regular physical activity of at least one hour daily.

NCEP STEP 1 DIET (STANDARD RECOMMENDATION)

The general dietary recommendations developed by the Institute of Medicine with the goal of promoting a healthy lifestyle will be reviewed for possible substitution for the NCEP guidelines below.

The following dietary recommendations were stated by the [National Cholesterol Education Program (NCEP)] in their monograph entitled 'The Third Report of the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), or ATP III'. The primary goal of these recommendations is to provide a diet that would reduce the risk of coronary heart disease in individuals with high LDL cholesterol levels. A secondary target of risk reduction, which was new to this version of the report, was the metabolic syndrome or insulin resistance.

Table 1: Nutrient Composition of the Therapeutic, Lifestyle Change, Diet, and Nutrient Recommended Intake

Saturated fat [a]	< 7% of total calories
Polyunsaturated fat	<10% of total calories
Monounsaturated fat	<20% of total calories
Total fat	25 - 35% of total calories
Carbohydrate [b]	50 - 60% of total calories
Fiber	20 - 30 g daily
Protein	Approximately 15% of total calories
Cholesterol	< 200 mg/day
Total calories [c]	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain.

a. Trans fatty acids are another LDL-raising fat that should be kept at a low intake.
b. Carbohydrates should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
c. Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

AMERICAN DIABETES ASSOCIATION (ADA) DIET RECOMMENDATION

Current evidence-based recommendations developed by the ADA are summarized in Table 2.

Table 2: American Diabetes Association (ADA) Diet (for Patients with Type 2 Diabetes)

Carbohydrates	a. Choose whole grains, fruits, vegetables, low-fat milk. b. Amount of carbohydrate is more important than source. c. Non-nutritive sweeteners in usual doses
Fats	a. Limit to 10% or less of total calorie intake. b. Limit cholesterol to <300 mg per day
Obesity and Weight Loss	a. Modest weight loss by reduced calorie intake improves insulin resistance. b. Structured programs of lifestyle change can produce weight loss of 5-7% calorie. c. Exercise and behavior modification are useful adjuncts to reduction of calorie intake.
Older Adults	a. Energy requirements decline with age. b. Encourage physical activity.
Hypoglycemia	Glucose is preferred treatment
Hypertension	a. Reduced sodium intake reduces blood pressure. b. Modest weight loss reduces blood pressure.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI) STEP I DIET RECOMMENDATION

Source: The Practice Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. NHLBI, 2000, p 27.

Table 3: NHLBI Step 1 Diet (for Weight Reduction)

Nutrient	Recommended intake
Calories [a]	Approximately 500 - 1,000 kcal/day reduction from usual state
Total fat [b]	30% or less of total calories
Saturated fatty acids [c]	8% - 10% of total calories
Monounsaturated fatty acids	Up to 15% of total calories
Polyunsaturated fatty acids	Up to 10% of total calories
Cholesterol [c]	< 300 mg/day
Protein [d]	Approximately 15% of total calories

Carbohydrate [e]	55% or more of total calories
Sodium chloride	No more than 100 mmol/day (approximately 2.4 g of sodium or approximately 6 g of sodium chloride)
Calcium [f]	1,000 to 1,500 mg/day
Fiber [e]	20 - 30 g/day

a. A reduction in calories of 500 to 1,000 kcal/day will help achieve a weight loss of 1 to 2 pounds/week. Alcohol provides unneeded calories and displaces more nutritious foods. Alcohol consumption not only increases the number of calories in a diet but has been associated with obesity in epidemiologic studies as well as in experimental studies. The impact of alcohol calories on a person's overall caloric intake needs to be assessed and appropriately controlled
b. Fat-modified foods may provide a helpful strategy for lowering total fat intake but will only be effective if they are also low in calories and if there is no compensation by calories from other foods
c. Patients with high blood cholesterol levels may need to use the Step II diet to achieve further reductions in LDL-cholesterol levels; in the Step II diet, saturated fats are reduced to less than 7 percent of total calories, and cholesterol levels to less than 200 mg/day. All of the other nutrients are the same as in Step I.
d. Protein should be derived from plant sources and lean sources of animal protein.
e. Complex carbohydrates from different vegetables, fruits, and whole grains are good sources of vitamins, minerals, and fiber. A diet rich in soluble fiber, including oat bran, legumes, barley, and most fruits and vegetables, may be effective in reducing blood cholesterol levels. A diet high in all types of fiber may also aid in weight management by promoting satiety at lower levels of calorie and fat intake. Some authorities recommend 20 to 30 grams of fiber daily, with an upper limit of 35 grams.
f. During weight loss, attention should be given to maintaining an adequate intake of vitamins and minerals. Maintenance of the recommended calcium intake of 1,000 to 1,500.

15.9 APPENDIX 9: INSTRUCTIONS FOR STANDARDIZED HIP CIRCUMFERENCE AND MINIMUM WAIST CIRCUMFERENCE MEASUREMENT

General Information:

Measurements should be taken after a fast of 8 or more hours (fasting measurements preferred, but non-fasting measurements will be accepted).

1. Participant should undress to underwear, such that the portion of the torso below the nipples and above the knee is visible to the person taking the measurement. Any outer clothing covering this portion of the body should be removed.
2. Use non-stretchable, cloth or vinyl measuring tape that measures in centimeters or millimeters and is at least one-half inch in width.
3. Make sure the tape does not compress the body tissues during the measurement.
4. Measuring tape should always be read at eye level at recorded to the nearest 0.1 cm.
5. All measurements should be made in triplicate and averaged. If one measurement varies more than 10% from the other two, it should be discarded and the remaining two values averaged.
6. Ask the participant not to hold in the stomach/to relax/exhale fully during the measurements.

Hip Circumference:

1. The participant should be standing erect but relaxed, with feet/ankles touching.
2. Viewing the participant from the side, visually identify the widest width of the hip, which is generally where there is maximal protuberance of the buttocks.
3. Measure circumference at that point, making sure the measuring tape is exactly parallel to the floor all the way around the body. Record the result in cm to the nearest millimeter/0.1 cm.
4. Repeat this procedure twice, with the participant fully exhaling between each measurement, so that in all 3 measurements are performed.
5. Follow instructions as per general information (Number 6), above.

Waist Circumference:

1. The participant should be standing erect but relaxed, with feet/ankles touching.
2. All measurements should be made after the participant has fully exhaled.
3. Viewing the participant from the front or rear, identify the smallest width of the waist;
4. measure circumference at that point. In each case, the measuring tape should be parallel to the floor during the measurement. Record the result in cm to the nearest millimeter/0.1 cm.
5. Repeat this procedure twice, with the participant fully exhaling between each measurement, so that in all 3 measurements are performed.
6. Follow instructions as per general information (Number 6), above.

15.10 APPENDIX 10: PROTOCOL AMENDMENT TEMPLATE

Amendment Details

History of Amendments

A total of two XX global amendments have occurred, as shown in the table below:

Document	Sponsor Approval Date (dd/mmm/yyyy)	Approximate No Enrolled*

*Subjects enrolled until the date of Sponsor approval date

Current Amendment

The table below provides an overview of the current amendment.

Amendment Number:	
Approximate No Enrolled	
Summary of the Amendment:	

Summary of Changes in the Current Amendment:

Section # and Name	Description of Change	Brief Rationale for Change

Other changes made throughout protocol:

- Editorial, grammatical, and typographical corrections were done in the text to provide better clarity to the readers.
- Relevant changes are also reflected in the synopsis

RESPONSIBILITY	**NAME**	**DATE AND SIGNATURE**
STUDY DIRECTOR: (SPONSOR'S REPRESENTATIVE)	**Deven V. Parmar MD, FCP** [redacted]	