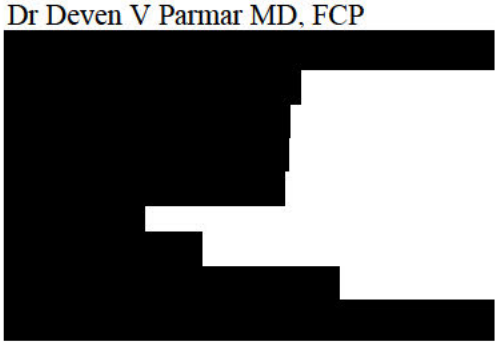
CLINICAL TRIAL PROTOCOL

Protocol No.	SARO.17.010
Version No. and dated	Version 7.0, dated 01 August 2019
Supersedes Protocol No.	SARO.17.010
Supersedes Version No. and dated	Version 6; 21 June 2019
IND Number	138352
Investigational Product(s)	Saroglitazar magnesium
Public Title	Safety, Tolerability and Efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with nonalcoholic fatty liver disease.
Scientific Title	A Phase 2A, single-center, open-label, single-arm, 24-week Study to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with nonalcoholic fatty liver disease.
Clinical Phase	2A
Sponsor	Zydus Discovery DMCC Unit No 909, Armada 2 Plot No: JLT-PH2-P2A, Jumeirah Lakes Towers Dubai UAE P.O Box 113536
Study Director: **(Sponsor's Representative)**	Dr Deven V Parmar MD, FCP 
Principal Investigator	

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Clinical Laboratory	[redacted]
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STUDY PROTOCOL SUMMARY

Name of Sponsor	Zydus Discovery DMCC Unit No 909, Armada 2 Plot No: JLT-PH2-P2A, Jumeirah Lakes Towers Dubai UAE P.O Box 113536
Name of the test product	Saroglitazar magnesium
Name of active ingredient of test product	Saroglitazar magnesium 4 mg
Name of the reference drug	Not Applicable
Name of active ingredient of reference product	Not Applicable
Potential Indication	Nonalcoholic fatty liver disease (NAFLD) in liver transplant recipients
Study Subjects	Liver transplant recipients with NAFLD
Number of Subjects	15 subjects
Clinical phase	2A
Trial Number	SARO.17.010
Date of Protocol	01 August 2019
Study Duration	33 Weeks
Treatment Duration	24 weeks

Study Title: A Phase 2A, single-center, open-label, single-arm, 24-week study to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with nonalcoholic fatty liver disease.

Objective: The objective of this study is to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium in liver transplant recipients with nonalcoholic fatty liver disease (NAFLD).

Primary Endpoint:

- To assess the safety of Saroglitazar magnesium 4 mg tablets in liver transplant recipients with NAFLD over 24 weeks of treatment.

Secondary Endpoints:

1. Changes in hepatic fat as determined by MRI-PDFF and MRE from baseline to End of treatment (EOT).
2. Changes in metabolic flexibility from baseline to EOT.
3. Changes in markers of insulin resistance [frequently sampled intravenous glucose tolerance test (FSIVGTT), glycosylated hemoglobin (HbA1c) and fructosamine] from baseline to EOT.
4. Changes in serum liver enzymes from baseline to EOT.
5. Changes in serum lipids from baseline to EOT.
6. Changes in atherogenic lipoprotein which includes small dense low-density lipoprotein (sdLDL), LDL size and concentration, subtypes of very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) from baseline to EOT
7. Change in Quality of life (QoL) score from baseline to EOT

8 Pharmacokinetics of Saroglitazar following first dose and last dose.
9 Body composition assessment via change in adipose tissue and skeletal muscle volume from baseline to EOT by whole body MRI.

Criteria for Safety:

1. Vitals: blood pressure (BP), pulse rate, oral temperature, respiratory rate.
2. The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems.
3. Body weight.
4. Laboratory assessment
   - Hematology: hematocrit, hemoglobin, mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, mean platelet volume (MPV), RBC count, white blood cell (WBC) count, differential WBC count.
   - Lipid profile: total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), VLDL and non-HDL.
   - Liver function tests (LFTs): aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (with Conjugated bilirubin), gamma-glutamyltransferase (GGT), total protein and albumin.
   - Amylase and lipase
   - Renal function tests (RFTs): blood urea nitrogen (BUN), serum creatinine and estimated glomerular filtration rate (eGFR).
   - Coagulation panel: activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT/INR), thrombin time (TT).
   - Immunosuppression level (tacrolimus, cyclosporine or sirolimus).
   - Gut hormones: Ghrelin, glucagon like peptide, leptin, resistin, and adiponectin
   - Glycemic control: HbA1c and fasting plasma glucose.
   - Urinalysis: urine examination: physical examination (appearance, color, specific gravity and pH); microscopy (epithelial cells, red blood cells, pus or white blood cells, casts and crystals) and chemical examination (protein, glucose, bilirubin, urobilinogen, ketone bodies, nitrite and blood); urine drug test (at screening).
   - Creatine phosphokinase (CPK), CK-MB, troponin 1 and NT-proBNP
   - Serum electrolytes: sodium, potassium, calcium, bicarbonate and chloride.
   - Serology: human immunodeficiency virus (HIV) type 1 and type 2, HAV IgM, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), CMV (IgG), and EBV VCAIgG
   - Pregnancy test: Serum pregnancy test and urine pregnacy test for women of childbearing potential.
5. Cardiac function: standard 12-lead electrocardiogram (ECG) and 2D echocardiogram (2D ECHO).
6. Adverse event(s): Frequency and severity of adverse events (AEs) /serious adverse events (SAEs), drop-outs due to AEs/SAEs for all subjects enrolled will be recorded. AE's will be assessed, and reported as appropriate, in accordance with applicable sections of the U.S. Code of Federal Regulations, Title 21 Part 312 for:
   - Causality (relatedness)
   - Severity
   - Seriousness
   - Expectedness

Inclusion Criteria:

Must meet all of the following conditions:

1. Able and willing to give written informed consent and comply with the requirements of the study protocol.
2. Male or female, 18 to 75 years of age, both inclusive.
3. Patients who are at least 6 months post liver-transplant with evidence of NAFLD in the liver graft.
4. Presence of NAFLD determined by Transient Elastography (TE) with a controlled attenuation parameter (CAP) score cut-off at 263 dB/m prior to enrollment.
5. Patients with ≤20% variation in the levels of ALT, AST, ALP and total bilirubin between Visit 1 and Visit 1.1, if either Visit 1 or Visit 1.1 laboratory results are elevated above the reference range.
6. History of medical compliance with immunosuppression.
7. Female subjects of non-child bearing potential or on highly effective contraception. For male subjects with female partners of childbearing potential, willing to follow highly effective contraception measures during the study, either by the male participant or his female partner or both.

Exclusion Criteria:

1. Pregnant or lactating females.
2. Patient with abnormal transaminases due to secondary intercurrent illness (should be determined over a period within last 12 months prior to screening).
3. Patients with clinically significant bile duct strictures as assessed with MRI and elevated liver enzymes during screening.
4. Recurrence of non-NASH causes of chronic liver disease after liver transplantation including autoimmune, viral, medications associated with steatosis and steatohepatitis (e.g., amiodarone and doxycycline) and alcoholic liver disease that are clinically active.
5. Graft cirrhosis as defined by:
   I. Cirrhosis on historical liver biopsy.
   II. Evidence of cirrhosis on imaging including portal venous collaterals.
   III. Prior history of decompensated liver disease including ascites, hepatic encephalopathy or variceal bleeding.
   IV. Evidence of esophageal varices on prior endoscopy.
6. Body mass index (BMI) <18 kg/m^2.
7. Subjects with change in body weight >5% in the 3 months prior to enrollment.
8. Subjects requiring corticosteroid or anticoagulation therapy.
9. History of myopathies or evidence of active muscle diseases.
10. Unstable cardiovascular disease, including:
    i. Unstable angina (i.e., new or worsening symptoms of coronary heart disease within the past 3 months), acute coronary syndrome within the past 6 months, acute myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months.
    ii. History of (within prior 3 months) or current unstable cardiac dysrhythmias.
    iii. Uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg.
    iv. Stroke or transient ischemic attack within the prior 6 months.
11. History of bladder disease and/or hematuria or has current hematuria unless due to a urinary tract infection.
12. Active malignancy post-liver transplantation.

13. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial non-melanoma skin cancer.
14. History of chronic rejection of liver transplant graft.
15. Acute cellular rejection of liver transplant graft within the past 6 months.
16. Evidence of Acute cellular rejection (ACR) or chronic rejection (CR) or alternative etiologies to NAFLD must be ruled out within 4-6 weeks prior to enrollment into the study by either a liver biopsy or at the discretion (clinical judgement and according to local standard of care) of the treating hepatologist.
17. Any of the following laboratory values:
    a. White blood cell count <2.5 x 10^3/uL
    b. Neutrophil count <1.5 x 10^3/uL
    c. Serum bilirubin >1.5 mg/dL
    d. Serum ALT >3X ULN
    e. INR >1.2
    f. Renal impairment as demonstrated by baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2
    g. Abnormal screening total creatine kinase
    h. Abnormal screening lipase or amylase
18. Poorly controlled diabetes as defined by an HbA1c >8.5% within the past 6 months.
19. Subjects with history of excessive alcohol intake, defined by ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to enrollment, where a "unit" of alcohol is equivalent to a 12 ounce (oz.) beer, 4 oz. glass of wine, or 1 oz. shot of hard liquor.
20. Subject tests positive for a urine drug screen.
21. Subject has a history of chronic (uncontrolled) pain.

Methodology

- This is a phase 2A, single-center, open-label, single-arm study evaluating the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg tablets in liver transplant recipients with NAFLD.
- This study will be initiated only after obtaining the approval of Independent Ethics Committee/Institutional Review Board (IEC/IRB), clinical trial permission from the applicable regulatory agencies and after registering the trial with clinicaltrials.gov.
- It is the responsibility of the Principal Investigator (PI) to ensure that the study is conducted in accordance with the protocol, with International Council for Harmonisation Good Clinical Practice (ICH-GCP), and with all other applicable regulatory requirements. Informed consent must be obtained from each study subjects before the start of any trial-related procedures.
- All laboratory reports should be reviewed by the PI and/or his/her designee and any abnormal findings should be addressed.
- All protocol deviations/violations occurring in the study shall be documented and informed to the Sponsor and to the IEC/IRB in accordance with their standard procedures.
- Participation in this study will last 33 weeks, which includes a 5-week Screening Period, a 24-week Treatment Period during which study drug will be administered and a 4-week Follow-up Period. The Screening Period may be extended under special circumstances with the explicit approval of the Sponsors' Medical Expert(s).

Study Schedules:

After signing the informed consent form (ICF), subjects will complete a screening visit which will include the following assessments: Demographic assessment, complete medical history, prior medications history, physical examination, vital signs, body weight and height measurement, laboratory assessments (i.e., hematology, lipid profile and lipoprotein, liver function test, renal function test, coagulation panel, HbA1c), viral serology, pregnancy test (for females of child-bearing potential), standard 12-lead ECG, AE assessment, urine analysis and urine drug (substance abuse) test. MRI (Whole Body and PDFF) and MRE will be performed at any point during screening but only after the assessment of Visit 1 laboratory results.

Liver enzymes (AST, ALT, ALP and total bilirubin) will be re-measured at least 4-week from Day -35 (Visit 1) to determine eligibility. The variation in the levels of the repeat measures of serum ALT, AST, ALP and total bilirubin at Day -7 (Visit 1.1) must be ≤20%, compared to the Day -35 (Visit 1) levels to be eligible for study entry, unless they are within the reference range.

After the Screening Period, the enrolment visit will occur at Day 1, study visits will occur on week 1, 4, 8, 12, 16, 20 and 24 with a Follow-up visit 4-week after the last dose of the study drug. Vital signs, targeted physical examination (lab results/signs/symptom driven), safety laboratory tests (i.e. hematology, coagulation panel, and immunosuppression levels, serum electrolytes, creatine phosphokinase, urine pregnancy test, fructosamine), dietary assessment, review of concomitant medications, AEs and glucometer assessment will be done as per table 1 (Schedule of Events). In addition, all the study assessments will be performed as per table 1 (Schedule of Events).

Eligible subjects will be enrolled. Prior to initial dosing, required Day 1 assessments will be performed and will include QoL assessment, targeted physical examination (lab results/signs/symptom driven), vital signs, laboratory assessments, pregnancy tests (for females of child-bearing potential), urine and blood collection for biomarker assessments and pharmacokinetic analyses, FSIVGTT, review of concomitant medications and AEs. A window of ±3 days will be given to perform all baseline assessments.

Pharmacokinetics of Saroglitazar will be assessed following first dose and last dose in liver transplant recipients with NAFLD. The samples will be collected at Pre-dose (0.0), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 24 hours post-dose. In addition, pre-dose sample will be collected at Visits 3, 4, 5, 6 and 7.

At the End of Treatment visit, all required parameters and assessments will be performed again.

Subjects will return for their final visit, the Follow-up visit, 4-week after the last dose of the study drug. At this visit assessments include a targeted physical examination (lab results/signs/symptom driven), vital signs, safety laboratory tests, a review of concomitant medications and AEs. A urine pregnancy test will be performed for females of child bearing potential only. All the study related procedures will be performed as per table 1 (Schedule of Events).

Unscheduled visits – Permitted at any time during the study for assessment and management of AEs and any concurrent clinical conditions. To be captured in the electronic case report form (eCRF).

- If further investigations are required in case of any AEs, PI will assess the AE and take necessary action, if required.

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

- Subjects that did not meet entry criteria but are enrolled into the study.
- Subjects that received the wrong treatment or incorrect dose.
- Subjects that received an excluded medication.
- Subjects that met the discontinuation criteria but continued in the study.
- Failure to report within specified timelines of the planned visits.
- Failure to perform a study procedure/assessment.
- IP non-compliance (<80% or >120%).

Subject withdrawal criteria:

- Subject who reports an SAE and if considered in PI or Medical Expert's opinion it is not in the subject's best interest to continue.
- Any subject found to have entered the study in violation of the protocol
- Termination of study by Sponsor or PI or the regulatory authorities or IEC/IRB.
- The subject is lost to follow-up.
- Any subject who wishes to withdraw his/her consent for participation in the study.
- In case a subject becomes pregnant, then she will be withdrawn from the study.

Discontinuation of patients from the Study Drug

1 Discontinue any patient with an AE of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher that is possible or probably drug related and discontinue any patient with an AE of CTCAE grade 4 regardless of attribution to study drug.

2 If any of the following criteria are met, the patient shall be immediately discontinued from drug and followed until resolution of adverse events and laboratory values shall be returned to baseline.
   a. Total bilirubin ≥3.0 mg/dL.
   b. Total CK >5 X ULN.
   c. Amylase or lipase >ULN.
   d. eGFR <60 mL/min/1.73 m^2 and where the value is reconfirmed after 24 hours repeat. Additionally, any subject who requires renal replacement therapy should also be discontinued from drug.
   e. Hemoglobin <10 mg/dL or hematocrit <30%; platelets <100,000/µL; WBC <4 x 10^3/uL.
   f. If troponin and CK-MB exceed the 99th percentile of the upper reference limit of the particular assay, serial labs should be obtained along with serial 12-lead ECGs, and cardiology should be consulted. If a patient has symptoms of dyspnea, edema, or a presumptive diagnosis of heart failure, NT-proBNP should be measured as close to the event as possible.

3 The criteria for discontinuing or temporarily interrupting study drug with close monitoring are as follows:
   a. When baseline measure (BLM) are <2x ULN, discontinue if ALT or AST increases >5x BLM.
   b. When the BLM ≥2X ULN but <5X ULN, discontinue if ALT or AST increases >3X BLM.
   c. When BLM ≥5X ULN, discontinue if ALT or AST increases >2X BLM.
   d. For ALT or AST increase >2X BLM accompanied by a concomitant total bilirubin increase to >2X BLM OR an INR increase by >0.2.

e. For elevations of liver enzymes accompanied by symptoms consistent with hepatic injury [e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)].
f. Temporarily interrupted treatment should be permanently discontinued for recurrence of laboratory abnormalities or symptoms following re-challenge.
g. If a patient lives in a remote area, testing can be performed locally and the results communicated to the PI site promptly.
h. If patients develop elevations of AST or ALT >2 times baseline measure or total bilirubin >1.5 times BLM while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2-3 times per week with or without drug discontinuation.

Concomitant Medication:

- Standard of care for patients with liver transplantation (LT) will be allowed. This includes changes in immunosuppression as necessary. Additionally, standard of care management of metabolic co-morbidities including hypertension, diabetes, hyperlipidemia will also be allowed. Patient with stable doses of statins (simvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin) or fibrates (clofibrate, fenofibrate) will be allowed; however, the dose should remain stable throughout the study period.

Restricted Medications:

- Patients are not permitted to take zileuton, vitamin E (>400 IU/day) or other drugs with potential effect on NAFLD/NASH such as ursodeoxycholic acid, S-adenosylmethionine (SAM-e), betaine, pentoxifylline.
- Patients are not permitted to take thiazolidinediones (pioglitazone, rosiglitazone), chemotherapy or other investigational medications during the study duration.
- Concomitant use of strong CYP2C8 Inhibitors/Substrates will be prohibited (Please refer Appendix 1.
- Patients also should not take any non-allowed over-the-counter medications or complementary and/or alternative medications.

Total Subjects:	A total 15 subjects will be enrolled in this study. Approximately 5 patients will be included in the pharmacokinetic study.
Test product: **Dose:** **Mode of administration:**	Saroglitazar magnesium 4 mg tablet once daily (OD) in the morning 60 minutes before breakfast without food Oral
Reference/Placebo therapy: **Dose:** **Mode of administration:**	Not applicable
Duration of treatment:	24 weeks
Criteria for efficacy	**Primary Endpoints:** The primary endpoint is to assess the safety of Saroglitazar magnesium 4 mg tablets in liver transplant recipients with NAFLD over 24 weeks of treatment. *Safety will be assessed during the study period through the reporting of AEs, and by clinical laboratory tests and vital sign assessment at various time points during the study.*

	Secondary Endpoints: Efficacy will be assessed through a number of exploratory endpoints. These include: 1 Changes in hepatic fat as determined by MRI-PDFF and MRE from baseline to EOT. 2 Changes in metabolic flexibility from baseline to EOT. 3 Changes in markers of insulin resistance FSIVGTT, HbA1c and fructosamine from baseline to EOT. 4 Changes in serum liver enzymes from baseline to EOT. 5 Changes in serum lipids from baseline to EOT. 6 Changes in atherogenic lipoprotein which includes sdLDL, LDL size and concentration, subtypes of VLDL and HDL from baseline to EOT. 7 Change in QoL score from baseline to EOT. 8 Pharmacokinetics of Saroglitazar following first dose and last dose in liver transplant recipients with nonalcoholic fatty liver disease. 9 Body composition assessment via change in adipose tissue and skeletal muscle volume from baseline to EOT by whole body MRI.
Criteria for Safety	1. Vitals: BP, pulse rate, oral temperature, respiratory rate 2. The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems 3. Body weight 4. Laboratory assessment o Hematology: Hematocrit, hemoglobin, MCHC, MCV, platelet count, MPV, RBC count, WBC count, differential WBC count o Lipid profile: TC, TG, HDL, LDL, VLDL and non-HDL. o Liver function tests : AST, ALT, ALP, GGT, total protein, albumin, total bilirubin (with Conjugated bilirubin). o Amylase and lipase o Renal function tests : Serum creatinine, eGFR and BUN. o Coagulation Panel: APTT, PT/INR, TT. o Immunosuppression level (tacrolimus, cyclosporine or sirolimus) o Gut hormones: Ghrelin, glucagon like peptide, leptin, resistin, and adiponectin o Glycemic control: HbA1c and fasting plasma glucose o Urinalysis: Urine examination: physical examination (appearance, color, specific gravity and pH); microscopy (epithelial cells, red blood cells, pus or white blood cells, casts and crystals) and chemical examination (protein, glucose, bilirubin, urobilinogen, ketone bodies, nitrite and blood); urine drug test (at screening)

	○ Creatine phosphokinase, CK-MB, troponin 1 and NT-proBNP ○ Serum electrolytes: sodium, potassium, calcium, bicarbonate and chloride ○ Serology: HIV type 1 and type 2, HAV IgM, HBsAg, HCV, CMV (IgG), and EBV VCAIgG ○ Pregnancy test: Serum pregnancy test and urine pregnancy test for women of childbearing potential 5. Cardiac function: standard 12-lead ECG and 2D ECHO 6. Adverse event(s): Frequency and severity of AE(s)/SAE(s), drop-out due to AEs/SAEs for all subjects enrolled will be recorded. AE's will be assessed, and reported as appropriate, in accordance with applicable sections of the U.S. Code of Federal Regulations, Title 21 Part 312 for: • Causality (relatedness) • Severity • Seriousness • Expectedness

Statistical Methods:
Safety Analysis: All safety data collected will be listed and be summarized, as appropriate, by treatment groups.

Efficacy analysis: Since the efficacy endpoints will be evaluated for exploratory purpose, formal statistical comparisons will not be made for these endpoints.

Exploratory analysis: Point estimates and 95% CI will be calculated for all continuous exploratory parameters (i.e. MRI-PDFF and laboratory values). For categorical variables, descriptive statistics will be calculated with count and percentage of subjects in each category by treatment group. Descriptive statistics will be provided for all pharmacokinetic parameters.
Sample Size: Due to exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof of concept studies.

ABBREVIATIONS

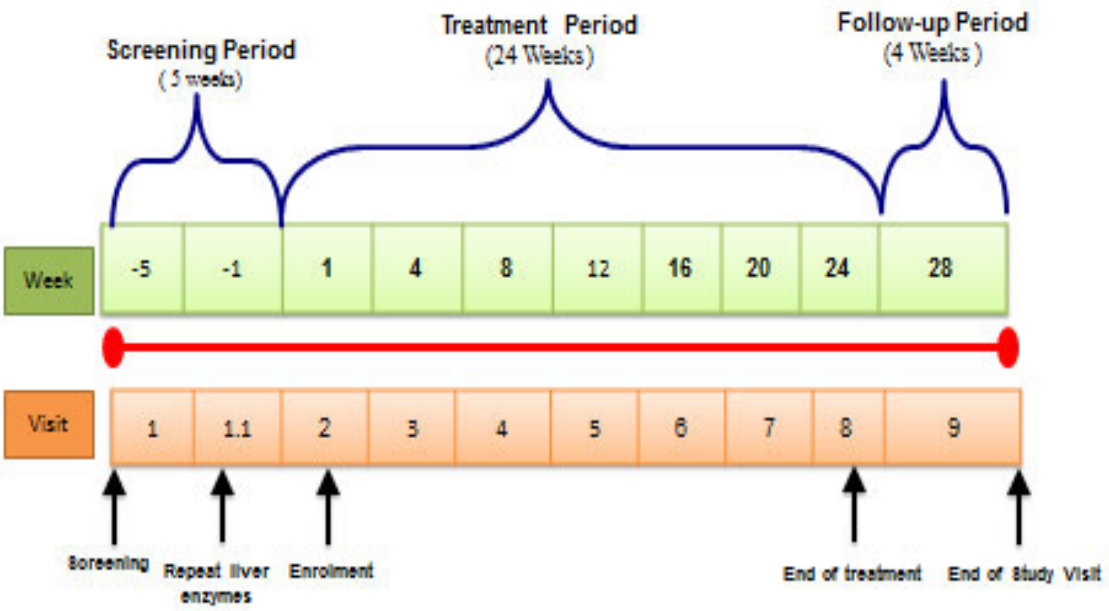
Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aP2	adipocyte fatty-acid-binding protein
API	active pharmaceutical ingredient
Apo	Apo lipoprotein
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLM	baseline measure
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CAP	Controlled Attenuation Parameter
CHL	Cadila Healthcare Limited
CPK	creatine phosphokinase
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
CYP	Cytochrome450
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EOT	End of treatment
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FA	fatty acids
FFA	Free fatty acid
FSIVGTT	frequently sampled intravenous glucose tolerance test
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HbA1c	glycosylated hemoglobin
HCV	hepatitis C virus
HDL	High-density lipoprotein
HIV	Human Immunodeficiency Virus
HBsAg	Hepatitis B surface antigen
ICF	Inform consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio

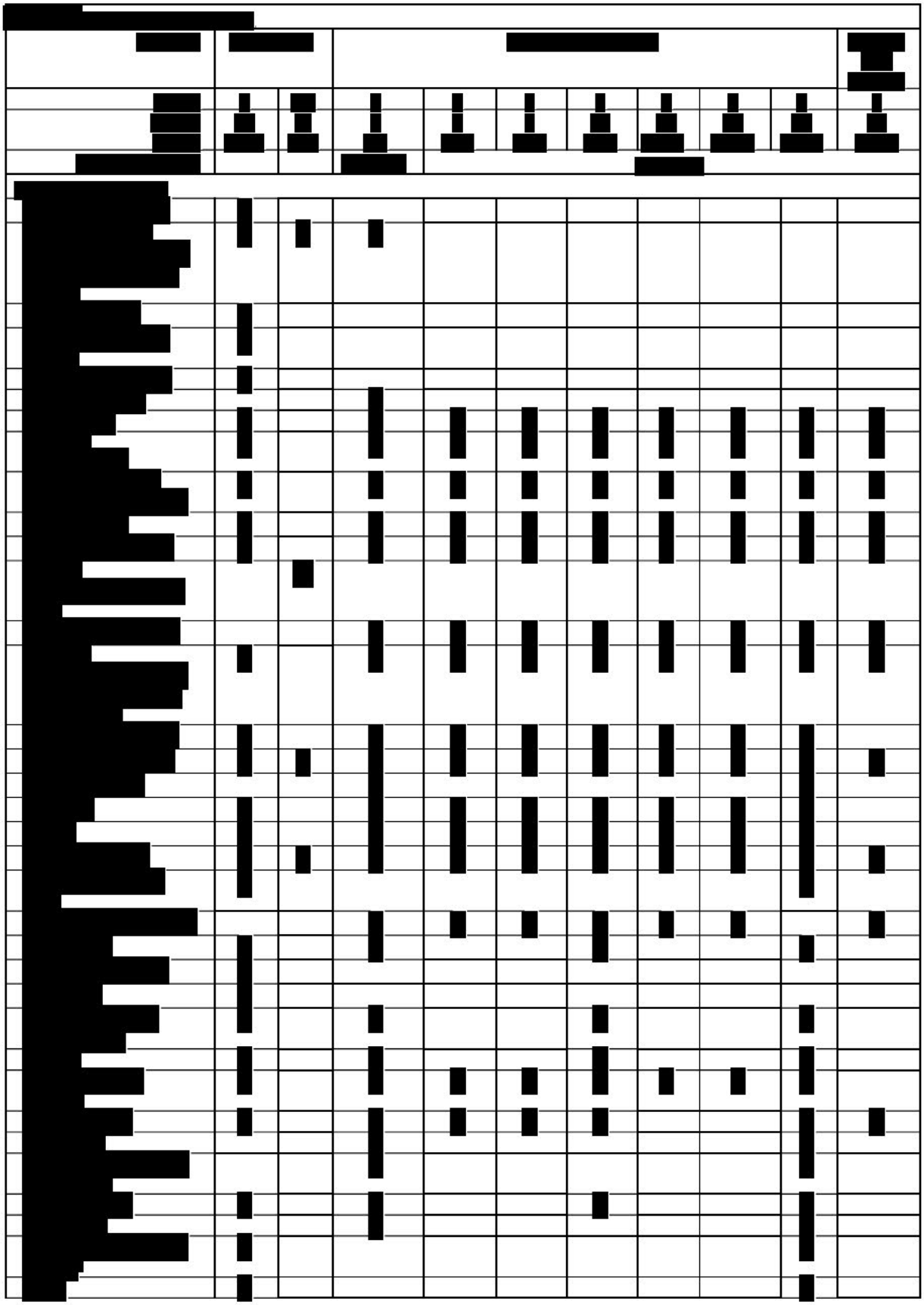
Abbreviation	Definition
IP	Investigational product
IRB	Institutional Review Board
LDL	Low-density lipoprotein
LFT	liver function test
LOCF	last observation carried forward
LPL	lipoprotein lipase
LT	liver transplantation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MITT	modified Intent-to-treat
MPV	mean platelet volume
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
MRE	magnetic resonance elastography
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NME	New molecular entity
OD	once daily
PP	per protocol
PPAR	peroxisome proliferator-activated receptors
PT	prothrombin time
QoL	Quality of life
RBC	red blood cell
RFT	renal function test
SAE	serious adverse event
SAP	Statistical Analysis Plan
sdLDL	small dense low-density lipoprotein
SOP	standard operating procedure
T2DM	Type 2 diabetes mellitus
TC	total cholesterol
TE	Transient Elastography
TG	Triglycerides
TT	thrombin time
TZDs	thiazolidinediones
VLDL	very low-density lipoprotein
WBC	white blood cell

TABLE OF CONTENTS

Contents

1 STUDY FLOW CHART





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2 INTRODUCTION

2.1 MEDICAL BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease (Angulo, 2002; Wieckowska and Feldstein, 2005) with an estimated global prevalence of 25% (Younossi et al., 2015). The severity of NAFLD ranges from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH) and around 7–30% have NASH, of which 10–20% progress to liver cirrhosis, for which the only treatment is liver transplantation (LT) (Younossi et al., 2015).

Non-alcoholic steatohepatitis is now the fastest growing and second most etiology of liver disease among new waitlist registrants for LT. Simultaneously to this course, the development and or recurrence of NASH after LT is certain to impose significant challenges. The genetic predisposition, immunosuppressive regimen and metabolic syndrome risk factors all play a role in the development of NAFLD/NASH after LT. In fact, NAFLD tends to recur 90% of the time after LT (Bhati et al. 2017) and patients with post-LT are at much higher risk of metabolic conditions such as diabetes, hypertension, hyperlipidemia and obesity. These metabolic conditions pose considerable risk to LT patients with NAFLD as these conditions or linked to post-LT mortality.

Generally, control of lipids and weight loss by diet and exercise are recommended for treatment of patients with NAFLD, including NASH, but their long-term effectiveness is questionable because many patients are unable to comply with the required dietary and lifestyle changes (Bellentani et al., 2008; Musso et al., 2010). Therefore, an alternative and effective pharmacotherapeutic approach is needed. Moreover, a multidisciplinary approach is required to manage transplanted patients with NASH, which include cardiovascular medicine, endocrinology, surgery, nutrition, and behavioral psychology, etc., to reduce identified risk factors.

2.2 RATIONALE FOR CONDUCTING THE STUDY

Saroglitazar magnesium is a novel predominately PPARα agonist and moderate PPARγ agonist. Pre-clinical studies with Saroglitazar magnesium using various animal models wherein, EC50 of PPARα: PPARγ >300; favorably modulated the lipid and glucose profile. Extensive preclinical safety pharmacology, pharmacokinetics and toxicological studies of

Saroglitazar magnesium showed favorable results. It was found to have superior or equivalent safety and efficacy profile compared to marketed fibrates or thiazolidinediones (TZDs) in pre-clinical studies.

PPARα activation by Saroglitazar magnesium increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of TG. This, in turn, increases diversion of FA from peripheral tissues (e.g., skeletal muscle and fat tissue) to the liver, thereby decreasing both FA synthesis and delivery of TG to peripheral tissues. In addition, Saroglitazar magnesium causes increased lipolysis and elimination of TG-rich particles from plasma by activating lipoprotein lipase (LPL) and reducing production of apolipoprotein C-III (an inhibitor of LPL activity). Consistent with the above mechanism, Saroglitazar magnesium was also found to reduce plasma LDL cholesterol. PPARα activation by Saroglitazar magnesium also induces an increase in the synthesis of apolipoproteins, A-I, A-II and HDL cholesterol.

Although Saroglitazar magnesium is predominantly a PPARα agonist, it also causes activation of PPARγ and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar magnesium increases the expression of numerous PPARγ-responsive genes involved in carbohydrate and lipid metabolism, including adiponectin, adipocyte fatty-acid-binding protein (aP2), LPL, fatty acid transport protein and fatty acid translocase (CD36). By increasing the expression of these genes, Saroglitazar magnesium decreases the post-prandial rise of plasma free fatty acids (FFA), improves post-absorptive insulin-mediated suppression of hepatic glucose output, reduces the metabolic burden on liver and muscle and promotes glucose utilization. Robust antidiabetic and insulin sensitizing effects of Saroglitazar magnesium were observed in preclinical models, in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues.

Peroxisome proliferator-activated receptors (PPARs), the largest family of nuclear receptors, are now a prime focus of NAFLD/NASH research. There are three subtypes, PPAR-α, γ and δ. Upon receptor activation, all bind the retinoid X receptor (RXR) to form transcriptionally active heterodimers. PPARα is primarily expressed in tissues that use fatty acids as a fuel, such as the liver, muscle, heart and kidneys. In contrast, PPARγ is found predominantly in adipose tissue where it mediates differentiation of pre-adipocytes (adipogenesis), lipid storage and insulin action.

PPARα is central to hepatic lipid homeostasis. When hepatic fatty acid levels increase, PPARα is activated, leading to transcription of such genes as liver fatty acid binding protein (LFABP), acyl-CoA oxidase (ACO), cytochrome P450 (CYP) 4A, microsomal triglyceride transfer protein (MTTP) and apolipoprotein B100 (apoB100). The net effect is catabolism and clearance of fatty acids. It has recently been appreciated that the liver may respond to newly synthesized fatty acids differently from those 'recycled' from peripheral stores, and this discrimination is mediated by selective effects on PPARα. This may explain why PPARα activation does not appear to occur as an adaptive response in fatty liver disease, when it would be an effective pathway to enhance insulin sensitivity and suppress inflammatory recruitment. Thus, while pharmacologic PPARα activation effectively 'cured' fibrosing steatohepatitis in a murine, dietary model, the efficacy of such agents is less clear in humans. PPARγ is found predominantly in adipocytes. It has both opposite and complementary functions to PPARα. Thus, PPARγ activation leads to differentiation of adipocytes from pre-adipocytes *in-vitro*. This increases the lipid storage capacity of the adipose mass, and in animals, also increases the number of small, insulin-sensitive adipocytes so as to improve insulin sensitivity. Increasingly, the importance of PPARγ is being recognized in the liver, despite the relatively low levels of expression normally found there. Steatosis is often associated with increased hepatocyte expression of PPARγ.

Therefore, peroxisome proliferator-activated receptor (PPAR) agonists are known to lower high blood triglyceride levels (PPARα agonists) and improve insulin resistance (PPARγ agonists), and may offer a potential treatment not only for patients with NAFLD or NASH but also for post liver transplant NAFLD/NASH.

2.3 DRUG PROFILE

Several research groups have developed or are attempting to develop dual PPARα/γ agonist, some of which may eventually reach desirable clinical efficacy and safety end point. But if the agonist has higher PPARγ binding properties then several of the side effects such as edema, weight gain, bone effects and cardiovascular complications may occur. Therefore, there has been an increasing interest to develop new molecular entities which can treat insulin resistance, lower plasma glucose in diabetic patients and improve lipid profile without weight gain and cardiovascular risk.

If a new Chemical Entity (NCE) having a superior PPAR-α agonist activity with a moderate PPAR-γ agonist activity is developed, it may have a more desirable clinical profile with no edema or weight gain effects. [redacted]

2.4 RISK AND BENEFIT

The safety and tolerability of Saroglitazar magnesium is well defined on the basis of pre-clinical and clinical studies (Phase 1 to Phase 3). This study will further evaluate the safety, tolerability and efficacy of Saroglitazar magnesium in liver transplant recipients with NAFLD. [redacted] Saroglitazar magnesium is approved in India at the doses of 2 mg and 4 mg QD for the treatment of "diabetic dyslipidemia" and "hypertriglyceridemia with type 2 diabetes mellitus (T2DM) not controlled by statin therapy". Overalll, Saroglitazar magnesium has shown to be well-tolerated during studies with no major safety concerns. Therefore we do not expect significant risk from the experimental medication. A theoretical benefit of participation is that treatment may improve NAFLD in liver transplant recipients. Though short-term treatment is of little consequence over the long term,

information about a given subject's response to this therapy could guide their clinician in making long-term therapeutic decisions. Thus, a potential benefit of the study is to determine the safety, tolerability and efficacy among subjects. As for risk, the protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate. On balance, we believe there is a reasonable prospect for individual and generalized benefit when compared to the risk of participation.

3 STUDY OBJECTIVES

The objective of this study is to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium in liver transplant recipients with NAFLD.

3.1 PRIMARY OBJECTIVE

To assess the safety of Saroglitazar magnesium 4 mg in liver transplant recipients with NAFLD over 24 weeks of treatment.

3.2 SECONDARY OBJECTIVES

1 Changes in hepatic fat as determined by MRI-PDFF and MRE from baseline to end of treatment (EOT).
2 Changes in metabolic flexibility from baseline to EOT.
3 Changes in markers of insulin resistance [frequently sampled intravenous glucose tolerance test (FSIVGTT), glycosylated hemoglobin (HbA1c) and fructosamine] from baseline to EOT.
4 Changes in serum liver enzymes from baseline to EOT.
5 Changes in serum lipids from baseline to EOT.
6 Changes in atherogenic lipoprotein which including small dense low-density lipoprotein (sdLDL), LDL size and concentration, subtypes of very low-density lipoprotein (VLDL), high-density lipoprotein (HDL) from baseline to EOT.
7 Change in Quality of life score from baseline to EOT.
8 Pharmacokinetics of Saroglitazar following first dose and last dose.
9 Body composition: changes in adipose tissue and skeletal muscle volume by whole body MRI.

3.3 SAFETY ASSESSMENT

1 Vitals: blood pressure, pulse rate, oral temperature, respiratory rate.
2 The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems.
3 Body weight.
4 Laboratory assessment

- Hematology: hematocrit, hemoglobin, mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, mean platelet volume (MPV), red blood cell (RBC) count, white blood cell (WBC) count, differential WBC count.
- Lipid profile: total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and non-HDL.
- Liver function tests (LFTs): aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (with Conjugated bilirubin), gamma-glutamyltransferase (GGT), total protein and albumin.
- Amylase and lipase
- Renal function tests (RFTs): blood urea nitrogen (BUN), serum creatinine, and estimated glomerular filtration rate (eGFR).
- Coagulation panel: activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT/INR), thrombin time (TT).
- Immunosuppression level (tacrolimus, cyclosporine or sirolimus).
- Gut hormones: Ghrelin, glucagon like peptide, leptin, resistin, and adiponectin
- Glycemic control: HbA1c and fasting plasma glucose.
- Urinalysis: urine examination: physical examination (appearance, color, specific gravity and pH); microscopy (epithelial cells, red blood cells, pus or white blood cells, casts and crystals) and chemical examination (protein, glucose, bilirubin, urobilinogen, ketone bodies, nitrite and blood); urine drug test (at screening).
- Creatine phosphokinase (CPK), CK-MB, troponin 1 and NT-proBNP.
- Serum electrolytes: sodium, potassium, calcium, bicarbonate and chloride.
- Serology: human immunodeficiency virus (HIV) type 1 and type 2, HAV IgM, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), CMV (IgG), and EBV VCAIgG.
- Pregnancy test: Serum pregnancy test and urine pregnacy test for women of childbearing potential.

5 Cardiac function: standard 12-lead electrocardiogram (ECG) and 2D echocardiogram (2D ECHO).

6 Adverse event(s): Frequency and severity of AEs /serious adverse events (SAEs), drop-outs due to AEs/SAEs for all subjects enrolled will be recorded. AE's will be assessed, and reported as appropriate, in accordance with applicable sections of the U.S. Code of Federal Regulations, Title 21 Part 312 for:

- Causality (relatedness)
- Severity
- Seriousness
- Expectedness

4 STUDY POPULATION

4.1 NUMBER OF SUBJECTS PLANNED

A total 15 subjects will be enrolled in this open-label, single-arm study to receive Saroglitazar magnesium 4 mg. Approximately 5 patients will be included in the pharmacokinetic assessment sub-study.

4.2 INCLUSION CRITERIA

1. Able and willing to give written informed consent and comply with the requirements of the study protocol.
2. Male or female, 18 to 75 years of age, both inclusive.
3. Patients who are at least 6 months post liver-transplant with evidence of NAFLD in the liver graft.
4. Presence of NAFLD determined by Transient Elastography (TE) with a controlled attenuation parameter (CAP) score cut-off at 263 dB/m prior to enrollment.
5. Patients with ≤20% variation in the levels of ALT, AST, ALP and total bilirubin between Visit 1 and Visit 1.1, if either Visit 1 or Visit 1.1 laboratory results are elevated above the reference range.
6. History of medical compliance with immunosuppression.
7. Female subjects of non-child bearing potential or on highly effective contraception. For male subjects with female partners of childbearing potential, willing to follow highly effective contraception measures during the study, either by the male participant or his female partner or both.

4.3 EXCLUSION CRITERIA

1. Pregnant or lactating females.
2. Patient with abnormal transaminases due to secondary intercurrent illness (should be determined over a period within last 12 months prior to screening).
3. Patients with clinically significant bile duct strictures as assessed with MRI and elevated liver enzymes during screening.
4. Recurrence of non-NASH causes of chronic liver disease after liver transplantation including autoimmune, viral, medications associated with steatosis and steatohepatitis (e.g., amiodarone and doxycycline) and alcoholic liver disease that are clinically active.

5. Graft cirrhosis as defined by:
   I. Cirrhosis on historical liver biopsy.
   II. Evidence of cirrhosis on imaging including portal venous collaterals.
   III. Prior history of decompensated liver disease including ascites, hepatic encephalopathy or variceal bleeding.
   IV. Evidence of esophageal varices on prior endoscopy.
6. Body mass index (BMI) <18 kg/m^2.
7. Subjects with change in body weight >5% in the 3 months prior to enrollment.
8. Subjects requiring corticosteroid or anticoagulation therapy.
9. History of myopathies or evidence of active muscle diseases.
10. Unstable cardiovascular disease, including:
    i. Unstable angina (i.e., new or worsening symptoms of coronary heart disease within the past 3 months), acute coronary syndrome within the past 6 months, acute myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months.
    ii. History of (within prior 3 months) or current unstable cardiac dysrhythmias.
    iii. Uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg.
    iv. Stroke or transient ischemic attack within the prior 6 months.
11. History of bladder disease and/or hematuria or has current hematuria unless due to a urinary tract infection.
12. Active malignancy post-liver transplantation.
13. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial non-melanoma skin cancer.
14. History of chronic rejection of liver transplant graft.
15. Acute cellular rejection of liver transplant graft within the past 6 months.
16. Evidence of Acute cellular rejection (ACR) or chronic rejection (CR) or alternative etiologies to NAFLD must be ruled out within 4-6 weeks prior to enrollment into the study by either a liver biopsy or at the discretion (clinical judgement and according to local standard of care) of the treating hepatologist.
17. Any of the following laboratory values:

a. White blood cell count <2.5 x 10^3/uL
b. Neutrophil count <1.5 x 10^3/uL
c. Serum bilirubin >1.5 mg/dL
d. Serum ALT >3X ULN
e. INR >1.2
f. Renal impairment as demonstrated by baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2
g. Abnormal screening total creatine kinase
h. Abnormal screening lipase or amylase

18. Poorly controlled diabetes as defined by an HbA1c >8.5% within the past 6 months.
19. Subjects with history of excessive alcohol intake, defined by ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to enrollment, where a "unit" of alcohol is equivalent to a 12 ounce (oz.) beer, 4-oz. glass of wine, or 1-oz. shot of hard liquor.
20. Subject tests positive for a urine drug screen.
21. Subject has a history of chronic (uncontrolled) pain.

4.4 WITHDRAWAL CRITERIA

The Investigator may withdraw a subject from the study for any of the following:

1 Subject who reports an SAE and if considered in Investigator or Medical Expert's opinion it is not in the subject's best interest to continue.
2 Any subject found to have entered the study in violation of the protocol.
3 Termination of the study by the Sponsor or Principal Investigator (PI) or the regulatory authorities or Independent Ethics Committee/Institutional Review Board (IEC/IRB).
4 The subject is lost to follow-up.
5 Any subject who wishes to withdraw his/her consent for participation in the study.
6 In case a subject becomes pregnant, then she will be withdrawn from the study.

4.4.1 Screen Failure

If a subject is termed as a screen failure for not meeting the inclusion/exclusion criteria, the subject may be rescreened only after obtaining Sponsor approval. The Sponsor may approve for rescreening those cases in which subjects failed the screening parameters within a narrow

margin. Screening laboratory tests may be repeated following the approval of the Sponsor or its designee if the laboratory test results seem implausible or inaccurate.

At least 35 days from the date of the subject's initial screening will need to elapse prior to rescreening a subject. The subject will need to be rescreened under a new screening number and a new informed consent must be obtained. A screen failure occurs when a patient who has signed the informed consent form (ICF) does not meet all the entry criteria outlined in this protocol and has not been randomized or received study drug. No study procedures (including End-of-treatment procedures) will be performed for these patients. For patients who fail to meet the inclusion criteria or who meet 1 or more of the exclusion criteria, the PI (or designee) will document on a screening log the reason for the screening failure.

4.5 HANDLING OF SUBJECT WITHDRAWAL

In case of withdrawal of consent, and unless otherwise stated by the subject in the withdrawal of consent, PI(s) will be encouraged to obtain information from the subject in order to follow the medical status of the subjects (especially when the subject withdraws his/her consent after having experienced an AE/SAE or an efficacy endpoint). Principal Investigator or designee(s) must make reasonable attempts (at least 3 attempts, one of which will be via a certified/traceable mail) to contact subjects that are lost to follow-up, in order to obtain health status and reason for withdrawal. These attempts must be documented in the medical records. In addition, if patient withdraws from the study, any data collected during the period of time will maintained as part of the study data.

5 STUDY TREATMENTS/IP MANAGEMENT

Saroglitazar magnesium 4 mg will be administered orally once daily (OD) in the morning 60 minutes before breakfast without food, for a period of 24 weeks.

5.1 TREATMENTS TO BE COMPARED

5.1.1 Investigational Product Description

The investigational product (IP) is Saroglitazar magnesium, which will be formulated as tablets, and will contain 4 mg of Saroglitazar magnesium and excipients.

The product that will be used in this study is outlined in Table 2.

Table 2 Identity of Study Drugs

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

[redacted]

5.1.2 Comparator Drug Description

Not Applicable.

5.2 DOSAGE AND TREATMENT SCHEDULE

Saroglitazar magnesium 4 mg will be given once daily orally in the morning 60 minutes before breakfast without food, for 24 weeks. However, on the day of the scheduled clinical visit, subjects will have the IP administered on site after fasting blood sample collection. If on the

day of a scheduled clinic visit the subject has already taken the IP, all procedures except blood sample collections will be performed. The subject will be asked to return in fasting condition the next day to have the blood sample collected, and will be reminded not to take the IP until after the blood sample collections. If the subject again returns having taken the IP, blood samples will be collected and the subject will be asked to return for the next scheduled visit.

5.3 PACKAGING, LABELLING AND SUPPLY

Tablets of Saroglitazar magnesium 4 mg will be packed, labeled and supplied by the Sponsor according to all local legal requirements. [redacted]. The investigator designee will confirm the receipt of IP in writing via fax/email.

The PI or designee will maintain an accurate record of the receipt of the study drug, including the dates received. Unused drug supplies will be returned to the Sponsor (or designee) for destruction/destroyed at the site after approval for the same by the Sponsor. No study drug will be destroyed or returned until complete drug accountability has been performed by the study monitor. All supplies must be accounted for at the end of the study period.

Investigational product must be dispensed to each subject in such a way that the subject can take the doses in accordance with the Protocol. A Drug Accountability Log(s) for recording the receipt, dispensing and return of the IP must be maintained by the PI or any designated personnel. The Drug Accountability Log(s) must be kept up to date and must be made available to the study monitor during monitoring visits.

5.4 STORAGE CONDITIONS AND STABILITY

Saroglitazar magnesium tablets will be stored at room temperature (20°C to 25°C or 68°F to 77°F) in a dry place away from light at the study site or pharmacy. If the IP temperature extends outside the 20-25°C range, a temperature excursion must be documented in the study-specific temperature log, and sent to the Sponsor. If the excursion is within 15-30°C, quarantine is not required, and the IP is acceptable for use. If the excursion is outside of the 15-30°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 $15\text{-}30^0$ C it will be considered as a

protocol deviation. Protect the IP from light. All IP supplies in the study will be stored in a secure location with access limited to the Site Pharmacist or the PI designated site staff.

5.5 BLINDING

This is an open-label study, therefore, PI and participants will be made aware what treatment they will be administered.

5.6 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUP

All subjects will receive Saroglitazar magnesium 4 mg. A screening number will be assigned at the site and will be used to identify the subject throughout the study and will be entered on all documentation. The Screening Number will be assigned in numerical order at the site. A subject number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment, or if a subject discontinues from the study, the Screening Number cannot be assigned to another subject.

Subjects will be considered randomized as soon as the first allocation treatment number/drug kit is assigned. The first study drug intake should take place as soon as possible after randomization (on the same day), under medical supervision. In the event a subject is randomized but is not administered study drug, this will be considered an early termination, not a screen failure. The randomization number and subject drug kit will not be reassigned to another subject.

5.7 SELECTION OF DOSES

Saroglitazar magnesium 2 and 4 mg have favorably modified the lipid profile and glycemia in the dyslipidemic patients with or without diabetes mellitus during its development in Phase 2 and 3 studies. Considering the efficacy, safety and tolerability of Saroglitazar magnesium, it is approved in India at the doses of 2 mg and 4 mg QD for the treatment of “Diabetic Dyslipidemia” and “Hypertriglyceridemia with T2DM not controlled by statin therapy”. Saroglitazar magnesium 4 mg dose has shown favorable effects on lipid profiles and on liver enzyme levels, therefore, this dose has been selected for this study.

5.8 CONCOMITANT MEDICATION

1. Standard of care for patients with LT will be allowed. These include management of immunosuppression per site’s transplant related protocol. Additionally,

management of metabolic co-morbidities such as diabetes, hypertension, hyperlipidemia and obesity will also be done as per local standard of care.

2. Patient with stable doses of statins (simvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, and rosuvastatin) or fibrates (clofibrate, fenofibrate) will be allowed in the study; however, their doses should remain stable throughout the study period.

5.8.1 Subjects on concomitant anti-diabetic medication

Patients on anti-diabetic medication must be assessed at scheduled visits for hyperglycemia/hypoglycemia; rescue medication will also be permitted, if required.

Patients on concomitant anti-diabetic medication will be provided with a glucometer and instructions for use. All point-of-care (POC) glucose measurements collected/documented by patients during the study period must be performed on the study-provided glucometer. The investigational site will download/record the data from glucometer/patient diary for assessment of glucose levels from the previous visit.

The patients should monitor their glucose levels as follows:

- Fasting blood glucose should be measured on at least two different days in a week. These measurements should be done in the morning before having breakfast and when the patient has been fasting for a minimum of 10 hours.
- Spontaneous measurements of blood glucose should be done in the event the patient suffers from suspected hypoglycemia. The PI or designee should inform the patients on recognizing the symptoms of hypoglycemia (i.e. palpitations, tremor, diaphoresis, hunger and/or cognitive impairment) and instruct them on the actions to be taken in accordance with standard-of-care.

  The American Diabetes Association (ADA) recommends the following treatment for non-severe hypoglycemia during which a patient is willing and able to consume oral treatment:

  1. Consume 15-20 grams of glucose or simple carbohydrates
  2. Recheck your blood glucose after 15 minutes
  3. If hypoglycemia continues, repeat #1 & #2
  4. Once your blood glucose returns to a normal level, consume a small snack if your next planned snack or meal is greater than 1 hour in the future.

Examples provided by the ADA of items containing 15 grams of simple carbohydrates include:

- Glucose tablets (follow instructions on the package)
- Gel tube (follow instructions on the package)
- 2 tablespoons of raisins
- 4 ounces (1/2 cup) of juice or regular (non-diet) soda
- 1 tablespoon of sugar, honey or corn syrup
- 8 ounces of nonfat or 1% milk
- Hard candy, gumdrops or jellybeans (read package for amount to consume)

In the event of severe hypoglycemia when a patient is unconscious and possibly seizing, and/or unable to safely ingest carbohydrates, do not attempt oral treatment. If glucagon is available, this should be administered as soon as possible. If glucagon is not available, it is not able to be administered or persons witnessing the event do not feel able to handle the situation, emergency medical personnel should be summoned via calling 911.

Principal Investigator will advise patients to report all hypoglycemic episodes occurring during the course of the study as they will be recorded in the electronic Case Report Form (eCRF).

Treatment for such conditions should be initiated as soon as the need for treatment is identified by the PI, in accordance with treatment guidelines and standard of care, and should be adjusted as necessary to treat the patient's condition(s). All treatment with these drugs must be recorded in the eCRF.

5.9 STOPPING RULE(S)

Safety and tolerability will be evaluated by the incidence, severity, and relationship to study intervention of any AEs and changes from baseline in laboratory test results, physical examination findings, and vital sign measurements, at any time after the subject has received study intervention. If continuous safety analysis reveals an adverse trend, the PI may halt the study independently, or in consultation with the IRB/Sponsor, as appropriate. Furthermore, if three or more subjects develop the same SAE related to the IP or a procedure, the study will be suspended until the safety review outcome, in consultation with the IRB/Sponsor.

5.9.1 Discontinuation of Patients from the Study Drug

1 Discontinue patient with an AE of CTCAE grade 3 or higher that is possibly or probably related to IP and discontinue patient with an AE of CTCAE grade 4 regardless of attribution to IP.

2 If any of the following criteria are met, the patient must be immediately discontinued from IP and followed until resolution of adverse events and laboratory values return to baseline/stable:-

   a. Total Bilirubin ≥3.0 mg/dL.

   b. Total CK >5 X ULN.

   c. Amylase or lipase >ULN.

   d. eGFR <60 mL/min/1.73 m^2 and where the value is reconfirmed after 24 hours repeat. Additionally, any subject who requires renal replacement therapy should also be discontinued from IP.

   e. Hemoglobin <10 mg/dL or hematocrit <30%; platelets <100,000/µL; WBC <4 x 10^3/uL.

   f. If troponin and CK-MB exceed the 99th percentile of the upper reference limit of the particular assay, serial labs should be obtained along with serial 12-lead ECGs, and cardiology should be consulted. If a patient has symptoms of dyspnea, edema, or a presumptive diagnosis of heart failure, NT-proBNP should be measured as close to the event as possible.

3 The criteria for discontinuing or temporarily interrupting study drug with close monitoring are as follows:

   a. When the baseline measurements (BLM) are <2x ULN, discontinue if ALT or AST increases to >5x BLM.

   b. When the BLM ≥2X ULN but <5X ULN, discontinue if ALT or AST increases to >3X BLM.

   c. When BLM ≥5X ULN, discontinue if ALT or AST increases to >2X BLM.

   d. For ALT or AST increases to >2X BLM accompanied by a concomitant total bilirubin increase to >2X BLM OR an INR increase by >0.2.

e. For elevations of liver enzymes accompanied by symptoms consistent with hepatic injury [e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)].
f. Temporarily interrupted treatment should be permanently discontinued for recurrence of laboratory abnormalities or symptoms following re-challenge.
g. If a patient lives in a remote area, testing can be performed locally and the results communicated to the PI/site promptly.
h. If patients develop elevations of AST or ALT >2 times baseline measure or total bilirubin >1.5 times BLM while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2-3 times per week with or without drug discontinuation.

5.9.2 Termination of Clinical Study

If the PI, the Sponsor or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, the clinical study may be terminated after appropriate consultation among the involved parties, the Sponsor or Principal Investigator (PI) or the regulatory authorities or Independent Ethics Committee/Institutional Review Board (IEC/IRB). Also, the clinical study may be terminated at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of a relevant unexpected or unacceptable risk to the patients enrolled in the clinical study;
- Three patients develop the same AE of CTCAE Grade 3;
- OR two patients develop any AE of CTCAE Grade 4;
- OR one patient develops an AE of CTCAE Grade 5;
- Failure to enroll patients at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the study drug.

Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and IP must be returned to the Sponsor. Any actions of the Contract

Research Organization required for assessing or maintaining patient safety will continue as required, despite termination of the study by the Sponsor.

5.10 RESTRICTED MEDICATIONS

- Patients are not permitted to take zileuton, vitamin E (>400 IU/day) or other drugs with potential effect on NAFLD/NASH such as ursodeoxycholic acid, S-adenosylmethionine (SAM-e), betaine, pentoxifylline.
- Patients are not permitted to take thiazolidinediones (pioglitazone, rosiglitazone), chemotherapy or other investigational medications during the study duration.
- Concomitant use of strong CYP2C8 Inhibitors/Substrates will be prohibited.
- Patients also should not take any non-allowed over-the-counter medications or complementary and/or alternative medications.

5.11 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 patient is indicated, including monitoring of vital signs and observation of clinical status.

[redacted]

[redacted].

5.12 TREATMENT COMPLIANCE

The patients will be asked to bring their bottles of the IP to the next visit; compliance for dosing will be assessed by examination of the bottles and tablet count by study personnel. Compliance will be documented on Individual drug accountability log(s). Study medication compliance <80% or >120% will be considered protocol deviations and require patients to be counselled on proper IP compliance.

6 OBSERVATIONS

6.1 SAFETY

6.1.1 Primary Endpoint

The primary endpoint is to assess the safety of Saroglitazar magnesium 4 mg tablets in liver transplant recipients with NAFLD over 24 weeks of treatment.

Safety will be assessed during the study period through the reporting of AEs, and by clinical laboratory tests and vital sign assessment at various time points during the study.

6.1.2 Medical History and Demographic Information

The medical history comprises:

- Complete medical history
- Medication history
- Reproductive history

The following demographic information will be recorded:

- Gender
- Age
- Ethnic origin
- Race
- Height, without shoes
- Body weight, without shoes
- BMI

6.1.2.1 Vital Signs

The following vital signs will be assessed at time points described in the Schedule of Assessments (Table 1):

- Sitting BP (systolic and diastolic; mmHg)
- Pulse (beats per minute)
- Oral body temperature (°F)
- Respiratory rate (breaths per minute).

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

6.1.2.2 Physical Examinations

Physical examination will be performed in accordance with the Schedule of Assessments (Table 1). The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems.

Patients' body weight will be recorded during all physical examinations. Height will be recorded at Screening Visit only.

6.1.3 Clinical Laboratory Assessments

All biological samples, with the exception of pharmacokinetic samples will be assayed at Institution laboratory by using analytical methods in compliance with standard and validated methodologies, with adherence to written standard operating procedures (SOPs) of the Institution throughout the study duration.

If multiple bioanalytical assay methods/local laboratories will be used, then cross-comparison among methods shall be performed to allow comparison of efficacy and safety parameters/values obtained by different assay methods. All laboratory tests done at the local laboratory will be per the site's policies and SOPs.

Details regarding the sample processing, handling, storage, and shipment of PK samples will be offered separately in the study-specific laboratory manual prior to the initiation of the trial.

6.1.3.1 Sample Collection

The total amount of blood drawn for each patient over the study will not exceed 500 mL. Multiple venipunctures should be avoided to collect blood samples. It is recommended to collect only 1 blood sample for efficacy and safety measurement at a given visit. Blood samples will be collected for clinical laboratory testing at the time points indicated in the Schedule of Assessments (Table 1). Safety laboratory variables are listed in below mentioned Table 3.

Table 3: Safety Laboratory Assessments

Hematology	Hematocrit, hemoglobin, MCHC, MCV, platelet count, MPV, RBC count, WBC count, differential WBC count **Coagulation Panel:** APTT, PT/INR ratio, TT.

Clinical chemistry	**Lipid profile:** TC, TG, HDL, LDL, VLDL and non-HDL. **Liver function tests:** AST, ALT, ALP, total bilirubin (with Conjugated bilirubin), GGT, total protein and albumin Amylase and lipase **Renal function tests:** BUN, serum creatinine, eGFR *eGFR will be calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.* **Creatine phosphokinase,** CK-MB, troponin 1 and NT-proBNP **Serum electrolytes:** sodium, potassium, calcium, bicarbonate and chloride **Gut hormones:** Ghrelin, glucagon like peptide, leptin, resistin, and adiponectin HbA1c and fasting plasma glucose
Serology	HIV type 1 and type 2 HAV IgM, HBsAg HCV Immunosuppression level (tacrolimus, cyclosporine or sirolimus) CMV (IgG), and EBV VCAIgG
Urinalysis	Physical examination (appearance, color, specific gravity and pH); microscopy (epithelial cells, red blood cells, pus or white blood cells, casts and crystals) and chemical examination (protein, glucose, bilirubin, urobilinogen, ketone bodies, nitrite and blood) Urine drug testing
Pregnancy test	Serum pregnancy test for women of childbearing potential at the Screening Visit 1, and Visit 8. Urine pregnancy test will be performed on Visit 2 to7 and Visit 9.

6.1.4 Twelve-lead Electrocardiograms and 2D ECHO

A standard 12-lead electrocardiogram will be performed locally at the study site in accordance with the Schedule of Assessments (Table 1). Twelve-lead electrocardiogram recordings will be taken in triplicate at the Screening Visit and as a single recording at all other applicable visits. A 5-minute rest period in between vital signs and ECG measurements is recommended. A 2D ECHO will be performed at baseline and end of the treatment visit.

6.1.5 Adverse events

Adverse event reporting will begin after the informed consent has been signed and will continue until end of follow-up period. The Common Terminology Criteria for Adverse Event (CTCAE) (Version 4.03 or higher) system will be used for reporting and grading AEs. Please refer Section 9.4 for details description.

All AEs will be captured in the AE eCRF. At a minimum, SAEs will be reported in the eCRFs as per the timelines defined in the Protocol in adverse event section.

Serious adverse events reporting must comply with the concerned regulatory requirements and IEC/IRB reporting requirements.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the PI that may make it infeasible to perform the test. In these cases, the PI will take all steps necessary to ensure the safety and well-being of the patient. When a protocol required test cannot be performed the PI will document the reason and the corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

6.2 EFFICACY

Efficacy will be assessed through a number of exploratory endpoints.

1 Changes in hepatic fat as determined by MRI-PDFF and MRE from baseline to EOT.
2 Changes in metabolic flexibility from baseline to EOT.
3 Changes in markers of insulin resistance FSIVGTT, HbA1c and fructosamine from baseline to EOT.
4 Changes in serum liver enzymes from baseline to EOT.
5 Changes in serum lipids from baseline to EOT.
6 Changes in atherogenic lipoprotein which includes sdLDL, LDL size and concentration, subtypes of VLDL and HDL from baseline to EOT.
7 Change in QoL score from baseline to EOT.
8 Pharmacokinetics of Saroglitazar following first dose and last dose in liver transplant recipients with nonalcoholic fatty liver disease.
9 Body composition assessment via change in adipose tissue and skeletal muscle volume from baseline to EOT by whole body MRI.

6.2.1 Magnetic Resonance Imaging-Derived Proton Density-Fat Fraction (MRI-PDFF)

The magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) is a novel imaging-based biomarker that allows fat mapping of the entire liver. Liver fat content will be measured using MRI-PDFF. Proton-density-fat-fraction technique is an MRI protocol that improves on the conventional Dixon in- and out-of phase method. PDFF uses a low flip angle to reduce T1 bias (Bydder M et al. 2008; Liu et al. 2007). Multiple echoes per excitation are used to correct T2* decay (Bydder M et al. 2008; Yokoo et al. 2009; Yu et al. 2007). As a

result, the expected loss of signal with longer echo times, particularly in the presence of iron, is corrected. In head-to-head comparisons, PDFF quantified liver fat more accurately than conventional two-point Dixon MRI (Yokoo et al. 2011; Mashhood et al. 2013). In addition, PDFF minimizes the multifrequency interference effects of fat protons (Yokoo et al. 2009). PDFF has been shown to have high reproducibility at 1.5 T and 3.0 T (Kang et al. 2011). Studies assessing liver fat have confirmed the accuracy of PDFF using hydrogen-1 MR spectroscopy (H1-MRS) (Yokoo et al. 2009; Yokoo et al. 2011; Kang et al. 2011; Noureddin et al. 2013) or liver histology (Idilman et al. 2013; Tang et al. 2013) as gold standard. In addition, PDFF MRI technique allows fat mapping for the entire liver, whereas longitudinal segmental changes of liver fat may be accurately determined and small differences can be detected (Noureddin et al. 2013). The procedure will be conducted per the site's policies and SOPs for the procedure which will be followed for the study.

6.2.2 Controlled Attenuation Parameter (CAP)

CAP based on FibroScan is a promising tool for noninvasive semiquantitative assessment of liver fat content (*De Ledinghen V, 2012)*. CAP measures the ultrasound attenuation at the center frequency of the FibroScan M probe (3.5 MHz), with values range from 100 to 400 dB/m. Besides CAP being able to provide an instantaneous assessment of liver steatosis, some advantages, such as quantificational accuracy and ease of performance (which provide for instantaneous results), as well as inexpensive cost and reproducibility are highlighted when compared with other imaging methods (*De Ledinghen V et al, 2014).* In a prospective study of 153 patients, the areas under the receiver operating characteristics curves of CAP for ≥5%, >33% and >66% steatosis were 0.79, 0.76 and 0.70, respectively (*Myers RP et al, 2012).*

See below table for vibration-controlled transient elastography cutoff values for CAP (Siddiqui et. al. CGH 2019). This table indicates 263 dB/m cutoff value to optimize sensitivity.

Steatosis grade: Non-event vs event	Prevalence of event	Cross-validated AUROC (95% CI)	Cut-off criteria	Cut-off (dB/m)	Sens	Spec	PPV	NPV
0 vs 1-3	95%	0.76 (0.64, 0.89)	Sens = 90%	263	0.90	0.35	0.96	0.15
			Spec = 90%	353	0.29	0.90	0.98	0.06
			Youden's index	285	0.80	0.77	0.99	0.16

0-1 vs 2-3	58%	0.70 (0.64, 0.75)	Sens = 90%	280	0.90	0.35	0.64	0.72
			Spec = 90%	367	0.20	0.90	0.70	0.46
			Youden's index	311	0.77	0.57	0.70	0.66
0-2 vs 3	27%	0.58 (0.51, 0.64)	Sens = 90%	274	0.90	0.20	0.29	0.84
			Spec = 90%	380	0.03	0.90	0.10	0.72
			Youden's index	306	0.80	0.40	0.32	0.85

6.2.3 Magnetic Resonance Elastography (MRE)

Magnetic resonance elastography (MRE) is a dynamic elasticity imaging technique that uses mechanical waves to quantitatively assess the shear modulus or stiffness of tissues (Muthupillai et al., 1995).

The three basic steps of this MRE are i) shear waves with frequencies ranging from 50 – 500 Hz are induced in the tissue using an external driver, ii) the waves are imaged inside the body using a special MRI technique and iii) the resulting data are processed to generate quantitative images displaying the stiffness of tissue. The procedure will be conducted per the site's policies and SOPs for the procedure which will be followed for the study.

6.2.4 Whole Body MRI

Body composition is linked to cardiometabolic health and will be evaluated in patients. Subjects will be scanned in a research-dedicated Phillips Ingenia 3.0T Omega HP Multi-Transmit MRI scanner using 6-minute dual-echo Dixen Vibe protocol, providing a water and fat separated volumetric data set covering neck to knees. Acquired images will be analyzed for visceral adipose tissue, subcutaneous adipose tissue, thigh muscle volume, and muscle fat infiltration in the anterior thighs. Liver fat content will be quantified via proton density fat fraction as published previously (Linge et. al, 2018).

6.2.5 Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)

The Frequently Sampled Intravenous Glucose Tolerance Test assesses insulin sensitivity by a computed mathematical analysis of glucose and insulin dynamics. FSIVGTT consists of an intravenously administered bolus of glucose and an infusion of insulin 20 minutes after

glucose injection. Blood samples are collected periodically for total test duration of 120 minutes. The procedure will be performed as per Institution standard operating guideline.

6.2.6 Metabolic Flexibility

Energy expenditure: The recording of the components of energy balance, i.e. energy intake and expenditure is extremely important to understand the individual's response to pharmacologic or lifestyle modifications interventions. Yet, estimation of energy expenditure by equations, and food dietary recording are imprecise and subject to recall bias, respectively. The indirect calorimetry technique, by measuring the oxygen consumption allows a precise measurement of energy expenditure; additionally, the measurement of carbon dioxide production provides the opportunity of measuring the respiratory quotient (RQ) and in turn calculating the substrate utilization (carbohydrate vs. fat). Virginia Commonwealth University has a newly established indirect calorimeters suite with two whole room indirect calorimeters, a small 4'x8' "flex room" for short term studies and a larger 10'x10' room, fitted with hospital bed, sink, and toilet which allows long-term studies. Additionally, recent improvements in the data acquisition algorithm allow the recording of acute changes in energy expenditure. By coupling minute by minute measurements of energy expenditure with wearable sensors able to capture spatial movements, researchers have the unique opportunity to precisely measure the energy expenditure in its components. Finally, by providing study meals with known calorie content and macronutrient composition researchers are also able to control the energy intake arm of the energy balance equation (Galgani and Ravussin, 2008).

Metabolic Flexibility: The switch from carbohydrate oxidation to lipid oxidation defined as a drop in RQ during an overnight fasting is one of the gold-standard measures to assess metabolic flexibility. Insulin-resistant and T2DM patients are characterized by a metabolic inflexibility, which is associated with even worse insulin resistance, and they typically present with an impaired drop in RQ overnight (higher RQ), defining metabolic inflexibility, and specifically metabolic inflexibility to lipids. A significant change in mean 14-hour RQ, as well as changes of the RQ area under the curve between baseline and the end of the intervention would suggest improvements in metabolic flexibility, which is associated with improved metabolic outcomes (Goodpaster and Sparks, 2017; Galgani et al., 2008).

6.2.7 Quality of Life Assessment

6.2.7.1 SF-36 Health Survey

Subjective QoL assessments will be measured using the SF-36 version 2.0, which is a 36-item patient response questionnaire that measures QoL across 8 domains, both physically and emotionally based. The 8 domains are physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health.

For information about the quality of life assessment, SF-36, version 2, refer to the SF-36.org Community at http://www.sf-36.org/tools/sf36.shtml.

6.2.8 Pharmacokinetics Assessment

Pharmacokinetics of Saroglitazar will be assessed following first dose and last dose in liver transplant recipients with NAFLD. The samples will be collected at Pre-dose (0.0), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 24 hours post-dose. In addition, pre-dose sample will be collected at Visits 3, 4, 5, 6 and 7. The sampling will be performed only in approximately 5 patients participating in the PK evaluation. A separate PK manual will be created describing the detailed procedures for PK sample handling, storage, shipment, bioanalysis, quality oversight and reporting of data.

The following pharmacokinetic parameters will be evaluated for first and last dose:

a. Peak plasma concentration (Cmax)
b. Time to reach peak plasma concentration (Tmax)
c. Area under plasma concentration vs. time curve till the last time point (AUC0-t)
d. Area under plasma concentration vs. time curve extrapolated to the infinity (AUC0-∞) after first dose
e. Area under plasma concentration vs. time curve in a 24 h dosing interval (AUCtau)
f. Elimination rate constant (λz)
g. Elimination half-life (t1/2)
h. Apparent volume of distribution (Vd/F)
i. Apparent clearance (CL/F)
j. Minimal or trough plasma concentration (Cmin) -for last dose only
k. Accumulation index calculated as a ratio of AUCtau (last dose)/AUCtau (first dose)

l. Fluctuation index

6.2.9 Appropriateness of Measurement

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

6.2.10 Abnormal Laboratory Findings

In addition, a clinically significant value outside the normal or reference range in a routine safety assessment, such as clinical laboratory, vital signs or standard 12-lead ECG, and 2D ECHO may signify an adverse finding. Additional examinations or repetition of test will be performed as medically indicated.

If the PI considers the abnormality as of major 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 PI or designee.

For any abnormal test result that meets one of the above conditions except for the last condition, the PI 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 severity, seriousness, duration, resolution, action taken and its association with the study treatment. The participant may be withdrawn or terminated from the study depending on the seriousness of the AE(s).

7 INVESTIGATIONAL PLAN

7.1 STUDY DESIGN AND PLAN

This study is designed to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium in liver transplant recipients with NAFLD.

1. This study will be initiated only after obtaining the approval of IEC/IRB and clinical trial permission from the applicable regulatory agencies.
2. It is the responsibility of the PI to ensure that the study is conducted in accordance with the protocol, with International Council for Harmonization Good Clinical Practice (ICH-GCP), and with all other applicable regulatory requirements. Informed consent must be obtained from each study subjects before the start of any study-related procedures.
3. All laboratory reports should be reviewed by the PI and/or his/her designee and any abnormal findings should be addressed.
4. All protocol deviations/violations occurring in the study shall be documented and informed to the Sponsor and to the IEC/IRB in accordance with their standard procedures.
5. This study consists of 3 Periods and a total 9 visits;
    a) 5-week Screening Period (Visit 1 and Visit 1.1)
    b) 24-week Treatment Period (Visit 2 to Visit 8)
    c) 4-week Follow-up Period (Visit 9)

7.2 STUDY PROCEDURES AT EACH VISIT

Study Schedules:

Visit 1, Screening Visit [Week -5; Day -35]

- All patient will be required to sign and date the IRB/IEC approved ICF after all study-related procedures have been explained by the PI/Designee and understanding the contents.
- Patients will be screened to participate in the study based on eligibility criteria.
- CAP
- MRI (Whole Body + PDFF) and MRE will be performed at any point during screening but only after the assessment of Visit 1 laboratory results. The same will be considered for the baseline assessment.

- Patients demographics, complete medical history and prior medication history will be recorded.
- Physical examination, height, body weight measurements, vital signs, laboratory assessments and standard 12-lead ECG recording will be performed to establish eligibility of the patient to participate in the study as per inclusion/exclusion criteria.
- All laboratory investigations will be carried out after at least 10-hour fasting.
- Laboratory parameters will be assessed as per Table 1 (Schedule of Events).
- Serum pregnancy test will be performed for females of child-bearing potential.
- AE assessment

Visit 1.1, Screening Visit [Week -1; Day -7]

- Liver enzymes (AST, ALT, ALP and total bilirubin) will be re-measured at least 4-week from Day -35 to determine eligibility. The variation in the levels of the repeat measures of serum ALT, AST, ALP and total bilirubin at Day -7 (Visit 1.1) must be ≤20%, compared to the Day -35 (Visit 1) levels to be eligible for study entry.
- AE assessment

Visit 2, [Week 1; Day 1(±3 Days)]

- Patients satisfying inclusion and exclusion criteria will be enrolled in the study.
- Concomitant medication will be recorded.
- Dietary assessment will be performed using Diet History Questionnaire (Appendix 2).
- Physical examination, vital signs, body weight measurements, 12-lead ECG and 2D ECHO will be performed.
- Metabolic flexibility and FSIVGTT will be performed.
- Baseline safety and efficacy evaluation will be performed as per Table 1 (Schedule of Events), including AE assessment. A window of ±3 days will be given to perform baseline assessments.
- Urine pregnancy test will be performed for females of child-bearing potential.
- Quality of life assessments (SF-36 Health Survey) will be performed.
- Pharmacokinetic samples will be drawn from applicable patients.
- Dispensing of IP for the next four weeks.
- Glucometer assessment for diabetic patient.

Visit 3, [Week 4; Day 29 (±3 Days)]

- Concomitant medication will be recorded.
- Physical examination, vital signs and body weight measurements will be performed.
- IP bottles will be collected by the PI or designee for checking the compliance.
- Dispensing of IP for the next four weeks.
- Safety evaluation will be performed as per Table 1 (Schedule of Events), including AE assessment.
- Pharmacokinetic sample will be drawn from applicable patients.
- Urine pregnancy test will be performed for females of child-bearing potential.
- Glucometer assessment for diabetic patient.

Visit 4, [Week 8; Day 57 (±3 Days)]

- Concomitant medication will be recorded.
- Physical examination, vital signs and body weight measurements will be performed.
- IP bottles will be collected by the PI or designee for checking the compliance.
- Dispensing of IP for the next four weeks.
- Safety evaluation will be performed as per Table 1 (Schedule of Events), including AE assessment.
- Pharmacokinetic sample will be drawn from applicable patients.
- Urine pregnancy test will be performed for females of child-bearing potential.
- Glucometer assessment for diabetic patient.

Visit 5, [Week 12; Day 85 (±3 Days)]

- Concomitant medication will be recorded.
- Physical examination, vital signs, body weight measurements and 12-lead ECG will be performed.
- Dietary assessment will be performed using Diet History Questionnaire (Appendix 2).
- IP bottles will be collected by the PI or designee for checking the compliance.
- Dispensing of IP for next four weeks.
- Safety and efficacy parameters will be assessed as per Table 1 (Schedule of Events), including AE assessment.
- Pharmacokinetic sample will be drawn from applicable patients.

- Urine pregnancy test will be performed for females of child-bearing potential.
- Quality of life assessments (SF-36 Health Survey) will be performed.
- Glucometer assessment for diabetic patient.

Visit 6, [Week 16; Day 113 (±3 Days)]

- Concomitant medication will be recorded.
- Physical examination, vital signs, and body weight measurements will be performed.
- IP bottles will be collected by the PI or designee for checking the compliance.
- Pharmacokinetic sample will be drawn from applicable patients.
- Dispensing of IP for next four weeks.
- Safety parameters will be assessed as per Table 1 (Schedule of Events), including AE assessment.
- Urine pregnancy test will be performed for females of child-bearing potential.
- Glucometer assessment for diabetic patient.

Visit 7, [Week 20; Day 141 (±3 Days)]

- Concomitant medication will be recorded.
- Physical examination, vital signs, and body weight measurements will be performed.
- IP bottles will be collected by the PI or designee for checking the compliance.
- Dispensing of IP for next four weeks.
- Safety and efficacy parameters will be assessed as per Table 1 (Schedule of Events), including AE assessment.
- Pharmacokinetic sample will be drawn from applicable patients.
- Urine pregnancy test will be performed for females of child-bearing potential.
- Glucometer assessment for diabetic patient.

Visit 8, [Week 24; Day 169 (±3 Days)]

- Concomitant medication will be recorded.
- Dietary assessment will be performed using Diet History Questionnaire (Appendix 2).
- Physical examination, vital signs, body weight measurements, 12-lead ECG, 2D ECHO, MRI (Whole Body + PDFF) and MRE will be performed.
- Metabolic flexibility and FSIVGTT will be performed.
- IP bottles will be collected by the PI or designee for checking the compliance.

- Safety and efficacy evaluation will be performed as per Table 1 (Schedule of Events), including AE assessment.
- Pharmacokinetic samples will be drawn from applicable patients.
- Serum pregnancy will be performed for female of child-bearing potential.
- Quality of life assessments (SF-36 Health Survey) will be performed.
- Glucometer assessment for diabetic patient.

Visit 9, [Week 28; Day 197 (±3 Days)]

- Concomitant medication will be recorded
- Physical examination, vital signs and body weight measurements will be performed.
- Safety parameters will be assessed as per Table 1 (Schedule of Events), including AE assessment.
- Urine pregnancy test will be performed for females of child-bearing potential.
- Glucometer assessment for diabetic patient.

Unscheduled visits

Unscheduled visits are permitted at any time during the study at the discretion of the PI or designee for assessment and management of AEs and any concurrent clinical conditions, Data will be captured in the eCRF.

If further investigations are required in case of any AE, PI will assess the AE and take necessary action, as required.

Immunosuppression levels will be monitored on Day -1, Day 1, Day 3, Day 7 and Weekly (Days 14, 21 and 28) for first month. If the Immunosuppression levels remain stable as per the opinion of the transplant hepatologist, they will then be monitored on a monthly basis (Days 57, 85, 113, 141 and 169) until the end of the study or as per the opinion of the transplant hepatologist/study investigator for clinical care.

If due to any reason after randomization, the patient discontinues the study before the End of Study Visit, all procedures of End of Study Visit (Visit 9) should be carried out.

7.3 ADHERENCE TO PROTOCOL

The PI and the site staff shall strictly adhere to the protocol and GCP guidelines. All patients will be strictly required to follow the instructions given to them as per this protocol. For any

deviation or violation from the protocol, considered serious, the patient may be withdrawn from the study at the discretion of the Sponsor or the PI.

7.4 PROTOCOL DEVIATION

For the purpose of this study, no distinction will be made between Protocol Violations and Deviations. Deviations will be categorized as Clinical Study Report (CSR) non-reportable protocol deviations and as CSR reportable protocol deviations. A CSR non-reportable protocol deviation includes any deviations that do not necessarily influence the results/outcome of primary endpoints or patient safety. A CSR non-reportable protocol deviation does not require immediate notification to the IEC/IRB, unless otherwise specified by IEC/IRB requirements. All CSR non-reportable protocol deviations will be noted in monitoring reports and provided to the PI by monitor.

A CSR reportable protocol deviation includes any violation that may influence the results/outcome of primary endpoints or patient safety. CSR reportable protocol deviations must be reported immediately to the IEC/IRB, as specified by the IEC/IRB requirements. All CSR reportable protocol deviations will also be reported to the Sponsor immediately. These deviations will also be noted in the monitoring reports and provided to the PI by monitor.

Note: Persistent non-compliance of CSR non-reportable protocol deviations may rise to the level of being considered CSR reportable protocol deviations (i.e., persistent non-compliance with dosing).

The Sponsor reserves the right to terminate the study at a given site in the event of monitoring and/or auditing findings of serious or persistent non-compliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by the PI/institution. In all cases of site closure due to protocol deviations, the IEC/IRB and regulatory authorities will be informed.

The CSR will provide the list of protocol deviation/violations in a separate section. The result will be analysed for all participants with CSR reportable protocol deviations.

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

- Patients that did not meet entry criteria but are enrolled into the study;
- Patients that received the wrong treatment or incorrect dose;
- Patients that received an excluded medication;
- Patients that met the discontinuation criteria but continued in the study;
- Failure to report within specified time lines of the planned visits;

- Failure to perform a study procedure/assessment;
- IP non-compliance (<80% or >120%).

7.5 DATA MONITORING COMMITTEE

As per DMC charter, an independent external Data Monitoring Committee (DMC) will monitor the study for safety events. The DMC will have a formal structure and will operate according to a previously agreed upon remit. Safety data will be reviewed regularly by a DMC. The DMC will meet on an ad hoc basis if there are at least 3 treatment-related AEs of CTCAE Grade ≥3 severity observed in the study. In the event of 2 similar treatment-related AEs of CTCAE Grade 4- or one treatment related AE of CTCAE Grade 5, the DMC will review the data and advise the Sponsor regarding stopping or continuing the study.

7.6 ADJUDICATION

An external independent Central Adjudication Committee (CAC) will adjudicate serious adverse events (SAEs), including all deaths, that are known or suspected to be a Major Adverse Cardiac Events (MACE) or heart failure hospitalizations. The CAC members will be independent of the Sponsor, the Data Monitoring Committee (DMC), and the clinical study sites and PI. A detailed CAC Charter and adjudication process will be described in a separate document.

8 BIOSTATISTICS AND DATA MANAGEMENT

8.1 STATISTICAL DESIGN

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® (version 9.4 or higher) (SAS Institute Inc., USA).

8.2 PLANNED ANALYSIS

8.2.1 Population

8.2.1.1 Safety population

The safety population includes all enrolled patients who received at least single dose of IP.

8.2.1.2 Modified intent-to-treat population (mITT)

The modified intent-to-treat (mITT) population includes:

1. All enrolled patients who received at least single dose of the IP.
2. Appear for at least one post baseline visit.

All secondary efficacy objectives will be analyzed using mITT population with post-baseline last observation carried forward (LOCF) as an imputation method for missing values.

8.2.1.3 Per-protocol population (PP)

The per-protocol population (PP) includes:

1. All enrolled patients who meet all the inclusion/exclusion criteria
2. Completed the study in compliance with the protocol
3. Do not have any major protocol violations

8.2.2 Primary Analysis

The primary endpoint is to assess the safety of Saroglitazar magnesium 4 mg tablets in liver transplant recipients with NAFLD.

Primary analysis will be carried out on safety population.

All AEs observed during the study period will be listed and assessed for causality, severity and seriousness. All AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) (version 19 or higher) by body system, frequency, severity, seriousness,

relationship to study drug and expectedness. Adverse events will be summarized by counts and percentages.

8.2.2.1 Secondary Analysis

Efficacy will be assessed through a number of exploratory endpoints which will be summarized at each time point, as appropriate.

Following secondary endpoints will be analyzed:

- Changes in hepatic fat as determined by MRI-PDFF and MRE from baseline to EOT.
- Changes in metabolic flexibility from baseline to EOT.
- Changes in markers of insulin resistance FSIVGTT, HbA1c and fructosamine from baseline to EOT.
- Changes in serum liver enzymes from baseline to EOT.
- Changes in serum lipids from baseline to EOT.
- Changes in atherogenic lipoprotein which includes sdLDL, LDL size and concentration, subtypes of VLDL and HDL from baseline to EOT
- Change in QoL score from baseline to EOT
- Pharmacokinetics of Saroglitazar following first dose and last dose in liver transplant recipients with nonalcoholic fatty liver disease (Descriptive statistics will be provided as detailed in Section 6.2.6).
- Body composition assessment via changes in adipose tissue and skeletal muscle volume from baseline to EOT by whole body MRI.

The change from baseline will be determined as:

Change = Post-baseline value – Baseline value.

Change from baseline for efficacy variables will be summarized appropriately.

All efficacy analyses will be based primarily on the mITT population and analyses based on the Per Protocol (PP) analysis set will be supporting.

All continuous efficacy exploratory parameters will be analysed and summarized appropriately. These analyses will also be supported by descriptive summaries (n, mean, standard deviation, median, minimum and maximum).

8.2.3 Safety Analysis

All safety analysis will be carried out on the safety population. The frequency tabulations of abnormal clinical laboratory values for the parameter will be presented by visit. All safety parameters (clinical laboratory testing, ECG, physical examination and vital signs) will be summarized using the following descriptive statistics: N, mean, median, standard deviation, minimum and maximum for continuous variables, and patient counts and percentages for categorical variables.

8.2.4 Baseline Characteristics

Demographic and baseline characteristics will be summarized as appropriate. Subject disposition and reason for withdrawal will be presented and summarized.

Unless otherwise stated, all the continuous variables will be represented by n, mean, standard deviation, minimum, median and maximum. All the categorical variables will be presented as counts and percentages.

8.2.5 Interim Analysis

No interim analysis is planned for the study.

8.2.6 Handling of Missing Data

Clarifications, wherever possible, will be obtained from the PI or designee for any missing data or for any illegible entry, unused or unauthenticated data and this will be recorded in the data handling report before the final database lock.

Patients who are discontinued from the study should be excluded from the PP analysis set. Any enrolled patient who is discontinued from the study for any reason and have at least a post-baseline efficacy data will be included in the mITT analysis set using post-baseline LOCF imputation method for missing values. No imputation method will be employed for drug concentration or PK parameters.

8.3 RANDOMIZATION

As this is a single-arm study, a randomization schedule is not required.

8.4 DETERMINATION OF SAMPLE SIZE

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of patients was chosen based on clinical experience with other similar proof of concept studies. Approximately 5 patients will be included in the pharmacokinetic assessment sub-study.

9 ADMINISTRATIVE MATTERS

The study will be carried out in compliance with the protocol, in accordance with the ICH Harmonised Tripartite Guideline for GCP and in accordance with applicable regulatory requirements.

9.1 ETHICS

9.1.1 Institutional Committee Review and Communications

The study will not be initiated before the protocol and the informed consent and patient information form have been reviewed and have received approval/favorable opinion from a registered IEC/IRB. Should a protocol amendment be made that requires central/IEC/IRB approval, the changes in the protocol will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval/favorable opinion from the IEC/IRB. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided that the appropriate regulatory authorities and IEC/IRB are notified as soon as possible (no longer than 5 days) and an approval is requested. Modification only for logistical or administrative changes may be implemented immediately; however, both the IRB/IEC and the Regulatory Authorities will be notified as soon as possible.

The constitution of the IEC/IRB must comply with the concerned regulatory requirements. A list of the IEC/IRB members, with names and qualifications, will be requested. If such a list is unavailable, the PI or designee must provide the name and address of the IEC/IRB along with a statement from the IEC/IRB that it is organised according to GCP and applicable laws and regulations. The IEC/IRB must also perform all duties outlined by the requirements of the regulatory agencies.

9.1.2 Informed Consent and Subject Information

Prior to patient participation in the study, written informed consent will be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of the participating country and site. Each signature must be dated by each signatory and the informed consent and any additional patient information form retained by the PI or designee as part of the study records. A signed copy of the informed consent and any

additional patient information must be given to each patient or the patient's legally authorised representative.

The patient must be informed that his/her medical records may be examined by authorised monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IEC/IRB members and by inspectors from regulatory authorities.

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

9.2 DATA MANAGEMENT AND RECORDKEEPING

9.2.1 Drug Accountability

Drug supplies, which will be provided by the Sponsor, must be kept in a secure, controlled access storage area under 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 PI and/or pharmacist must maintain records of the product's delivery to the study site, the inventory at the site, the dispensation to each patient, 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 PI or designee will maintain records that document adequately that the patients 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 PI or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the PI or site's possession.

9.2.2 Data Management

9.2.2.1 Data Handling

Data will be recorded by the PI or designee into eCRFs 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. An eCRF will be considered

complete when all missing, incorrect, and/or inconsistent data has been accounted for, and the eCRF is signed by the PI.

9.2.2.2 Computer Systems

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

9.2.2.3 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.

9.2.2.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for AEs and medical history, and
- WHO Drug Dictionary for prior and concomitant medications.

9.2.2.5 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 eCRFs must be reviewed and approved/signed by the PI.

9.2.3 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the PI's site. Data reported on the eCRFs must be consistent with the source documents or the discrepancies must be explained. The PI or designee may need to request previous medical records or transfer 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 eCRF should be included and derived from source documents:

- Subject identification (subject number, gender, date of birth/age)
- Subject participation in the study (subject number, date informed consent given)
- Dates of subject's visits
- Medical history
- Medication history
- AEs (onset and end)
- SAEs (onset and end)
- Originals or copies of laboratory results: All laboratory reports must be reviewed by the PI and/or his/her designee; any abnormal findings should be addressed.
- Conclusion of subject's participation in the trial.

9.2.4 Direct Access to Source Data/Documents

The PI/institution will permit study-related monitoring, audits, IEC/IRB reviews and regulatory inspections by providing direct access to all related source data/documents. 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(s), auditor(s) and inspection by applicable regulatory authorities. The on-site monitor will review all eCRFs and ICFs. The accuracy of the data will be verified by reviewing the documents described in Section 9.2.3.

All ECG's will be conducted locally. A photocopy should be made of the ECG, and assessment of clinical significance should be conducted by site staff personnel delegated to do so.

9.2.5 Trial Monitoring

It is the responsibility of the Principal Investigator to ensure that the study is conducted in accordance with the protocol, with ICH GCP, and with all other applicable regulatory requirements and that valid data are entered into the eCRFs.

To achieve this objective, the study monitor's duties are to aid the PI, and at the same time, the Sponsor in the maintenance of complete, legible, well-organized and easily retrievable data. Before the enrolment of any subject in this study, the Sponsor or their designee will review with the PI and site personnel the following documents: protocol, Investigator's

Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The PI 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 eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the monitor will review the data 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 PIs. The PI 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.

9.3 QUALITY ASSURANCE AUDIT

A quality assurance audit of this study may be conducted by the Sponsor or Sponsor's designees. The quality assurance 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 trial.

9.4 PROCEDURES

9.4.1 Adverse Events

All AEs occurring during the course of the clinical trial from the signing of the informed consent onwards will be collected, documented, and reported to the Sponsor by the PI or designee according to the specific definitions and instructions detailed in this section.

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Any medical condition already present at screening should not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g. electrocardiogram) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs. The PI will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

9.4.2 Serious Adverse Events

A serious adverse event is any AE occurring at any dose or during any use of Sponsor's product 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 patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious Adverse Event Reporting-Procedures for Investigator:

Initial Reports:

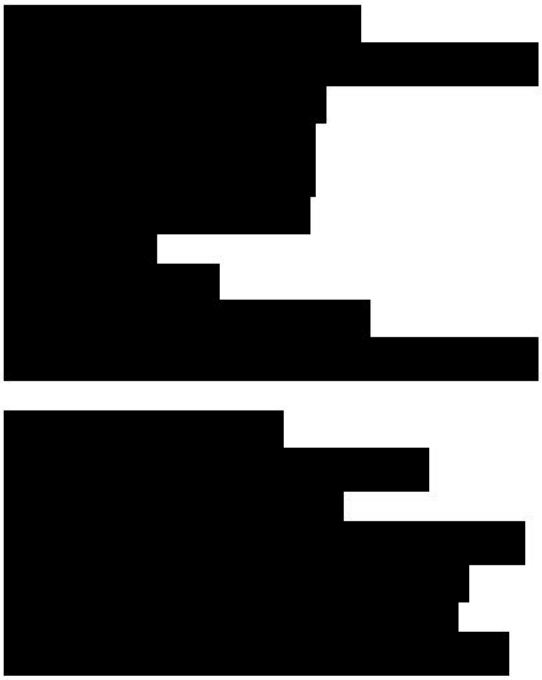
Any SAE, or follow-up to a SAE, including death due to any cause that occurs to any subject from the time the consent is signed through 4-week following cessation of treatment, whether or not related to the Sponsor's product, must be reported to the Sponsor within 24 hours of the knowledge of the occurrence to investigational site.

Additionally, any SAE, considered by the PI or designee, who is a qualified physician, to be related to the Sponsor’s product, that is brought to the attention of the PI or designee at any

time outside of the time-period specified in the previous paragraph also must be reported immediately to the Sponsor.

To report an SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. Once the form is completed, the CRO/Sponsor Safety personnel will be notified electronically. If the event meets serious criteria, and, it is not possible to access the EDC system, send an email to CRO/Sponsor or call the CRO/Sponsor SAE hotline (phone number listed below), and email the completed SAE form/information to CRO/Sponsor (email listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:



Follow-Up Reports

All patients with SAEs must be followed-up for outcome. Within 24 hours of receipt of follow-up information, the PI or designee must update the SAE form electronically in the EDC system and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Sponsor Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.4.3 Follow-up of Adverse Events

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

9.4.4 Evaluating Adverse Events

Each AE will be assessed by the PI or a medically-qualified investigator with regard to the following categories:

Severity

The PI or designee will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. The Common Terminology Criteria for Adverse Event (CTCAE) (Version 4.03 or higher) system will be used for reporting and grading AEs severity of events not classified in CTCAE 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 patient's normal daily activities.
- Moderate: Event introduces a low level of inconvenience or concern to the patient 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 patient's normal daily activities and generally requires systemic drug therapy or other treatment. Severe events are usually incapacitating.

Causality

For all AEs, the PI or designee will provide an assessment of causal relationship to study drug. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF.

Causal relationship will be classified according to the following criteria:

- Unrelated

- Possibly related: Suggests that the association of the AE with the study drug is unknown. However, the AE is not reasonably supported/explained by other conditions.
- Probably related: Suggests that a reasonable temporal sequence of the AE with study drug administration exists and, based upon the PI's clinical experience, the association of the AE with study drug seems likely.
- Definitely related: Suggests that a causal relationship exists between the study drug and the AE, and other conditions (concomitant illness, progression or expression of the disease state, reaction to concomitant medication) do not appear to explain the AE.
- Unknown

Outcome

Outcome of AEs will be defined according to the International Council for Harmonisation (ICH) Topic E2B, ICH Guideline, as follows:

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Not Recovered/Not Resolved
- Fatal/results in death
- Unknown

9.4.5 Expected Adverse Events

Adverse events reported by 2% or more patients treated with Saroglitazar magnesium during the double-blind, active-controlled study with pioglitazone as the comparator regardless of causality included gastritis and asthenia. In the double-blind placebo controlled study, AEs reported by 2% or more patients treated with Saroglitazar magnesium included gastritis, dyspepsia, pyrexia and pain. The details of AE(s) experienced during the Saroglitazar magnesium studies are mentioned in the IB. Principal Investigator(s) are advised to provide protocol education for patients and caregivers for potential symptoms of adverse effects that should be reported to the site/PI, such as skeletal muscle pain, weight gain, peripheral edema, shortness of breath, hypoglycaemia, etc.

9.4.6 Pregnancy

At the Screening Visit and the End of treatment Visit every female subject of childbearing potential will be tested for serum pregnancy test and urine pregnancy test will be performed at other visits. Women are advised not to become pregnant during the study and for at least 4-week after the end of the treatment period. Adequate contraceptive measures shall be used to prevent pregnancy. Even when contraceptive methods are used, there is a small risk that pregnancy might occur. In case a patient becomes pregnant, then she will be withdrawn from the study and adequate monitoring of the patients will be conducted.

Although pregnancy and lactation are not considered AEs, it is the responsibility of the PI or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the study. All patients 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.

The PI or designee should report the pregnancy to the Sponsor within 24 hours of being notified. The Sponsor will then forward the completed Exposure-in-Utero form to the PI.

9.5 RULES FOR AMENDING PROTOCOL

All amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol and then will be submitted to Regulatory Authorities/IEC/IRB. Modification only for logistical or administrative changes may be implemented immediately; however, both the IEC/IRB and the Regulatory Authorities will be notified immediately.

9.6 FINANCIAL DISCLOSURE

The PI and sub-investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfil their obligations. In addition, the PI/sub-investigator must commit to promptly update this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

9.7 STATEMENT OF CONFIDENTIALITY

Individual subject 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, to the IEC/IRB and the regulatory authorities as required under the law. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

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

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

9.8 FINAL REPORT AND PUBLICATION POLICY

A report will be prepared by the Sponsor. It will include the tabulated raw data and the biostatistical report on the data.

Zydus Discovery DMCC is, as much as possible, dedicated to support the process of free exchange of relevant scientific information. Any publication of the results of this study must be consistent with the ZYDUS publication policy. The rights of the PI and of the Sponsor with regard to publication of the results of this study are described in the Investigator agreement.

9.9 ARCHIVING

Subject's files, identification codes and other source data (including original reports of test results, dispensing logs and records of informed consent), IEC/IRB approval letter, correspondence and other documents pertaining to the conduct of the study will be kept as per the SOPs of the institution. No document pertinent to the study shall be destroyed without prior written agreement between the Sponsor and the PI. All documents should be preserved safely after the completion/termination of the study for at least a period of 5 years if it is not possible to maintain the same permanently.

10 REFERENCES

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11 APPENDICES

Appendix 1: List of Known CYP2C8 Inhibitors/Substrates

Selected inducers, inhibitors and substrates of CYP2C8		
Substrates	**Inhibitors**	**Inducers**
• amodiaquine[a] (antimalarial, anti-inflammatory) • cerivastatin[a] (statin) • enzalutamide (antiandrogen) • paclitaxel[a] (chemotherapeutic) • repaglinide[a] (antidiabetic) • torasemide[a] (loop diuretic) • sorafenib[a] (tyrosine kinase inhibitor) • rosiglitazone (antidiabetic) - converted to active metabolites[b] • buprenorphine (semisynthetic opioid) • polyunsaturated fatty acids • montelukast (leukotriene receptor antagonist)	**Strong** • gemfibrozil[a] (hypolipidemic) **Moderate** • trimethoprim[a] (antibiotic) **Unspecified potency** • thiazolidinediones[a] (antidiabetic) • montelukast[a] (leukotriene receptor antagonist) • quercetin[a] (antiinflammatory)	**Unspecified potency** • rifampicin[a] (antibiotic)

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

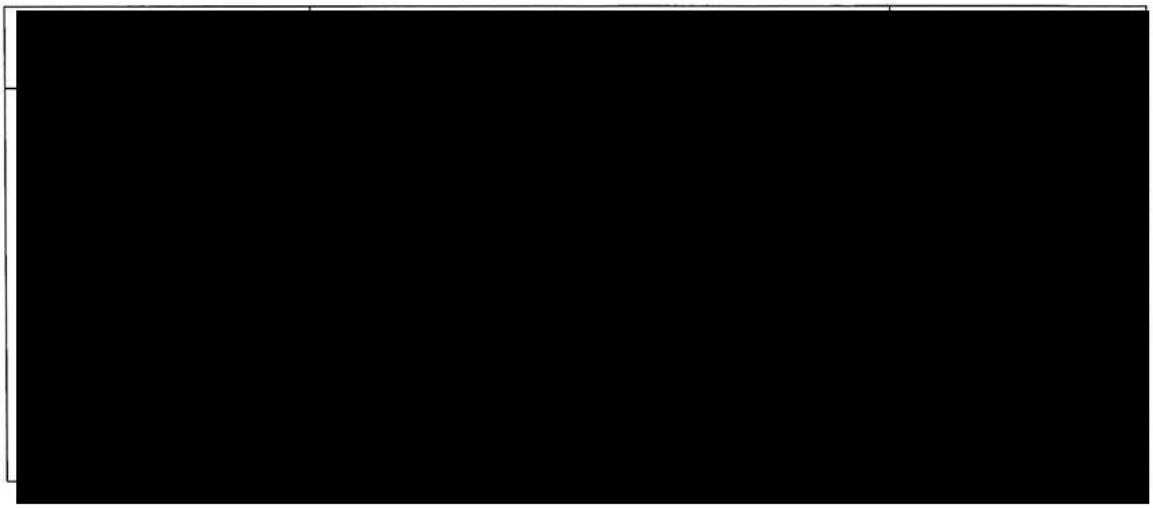
b Chapter 26 in: Rod Flower; Humphrey P. Rang; Maureen M. Dale; Ritter, James M. (2007). Rang & Dale's pharmacology. Edinburgh: Churchill Livingstone. ISBN 0-443-06911-5

Appendix 2: NATIONAL INSTITUTES OF HEALTH- Diet History Questionnaire

(https://epi.grants.cancer.gov/dhq2/forms/)

12 SIGNATURE PAGE

Protocol Title: A phase 2A, single-center, open-label, single-arm, 24-week study to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with nonalcoholic fatty liver disease.



SPONSOR APPROVAL

STUDY TITLE: A phase 2A, single-center, open-label, single-arm, 24-week study to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with nonalcoholic fatty liver disease.

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.

DECLARATION OF PRINCIPAL INVESTIGATOR

STUDY TITLE: A phase 2A, single-center, open-label, single-arm, 24-week study to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium 4 mg in liver transplant recipients with nonalcoholic fatty liver disease.

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) or Institutional Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, 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]