Clinical Study Protocol NCT03061721

A Phase 2, Prospective, Multicenter, Double-blind, Randomized Study of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg Versus Placebo in Patients with Nonalcoholic Fatty Liver Disease and/or Nonalcoholic Steatohepatitis

Sponsor:

Zydus Discovery DMCC
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Zydus Study No.: SARO.16.005
Zydus Protocol No.: SARO.16.005.03.PROT
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IMP Name: Saroglitazar Magnesium
IND No.: IND 128791
Development Phase: Phase 2
Date of Final Protocol: 26 March 2018

The study will be conducted according to the protocol and in accordance with the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (E6-R2) and with other applicable regulatory requirements.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor

Protocol Title: A Phase 2, Prospective, Multicenter, Double-blind, Randomized Study of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg Versus Placebo in Patients with Nonalcoholic Fatty Liver Disease and/or Nonalcoholic Steatohepatitis.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (E6-R2) and with other applicable regulatory requirements applicable to this clinical study.

[redacted]

26 Mar 2018

Date

COORDINATNG INVESTIGATOR SIGNATURE PAGE

Declaration of the National Coordinating Investigator

Protocol Title: A Phase 2, Prospective, Multicenter, Double-blind, Randomized Study of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg Versus Placebo in Patients with Nonalcoholic Fatty Liver Disease and/or Nonalcoholic Steatohepatitis.

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the International Council for Harmonisation Tripartite Guideline for Good Clinical Practice (E6-R2) and with other applicable regulatory requirements applicable to this clinical

[redacted]

NOV 27, 2017

Date

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Declaration of the Site Principal Investigator

Protocol Title: A Phase 2, Prospective, Multicenter, Double-blind, Randomized Study of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg Versus Placebo in Patients with Nonalcoholic Fatty Liver Disease and/or Nonalcoholic Steatohepatitis.

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, electronic Case Report Forms (CRFs) and other scientific data.

The study will not be commenced without the prior written approval of Institutional Review Board (IRB) or Independent 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 have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Principal Investigator

Signature	Date
Printed Name	
Title	

LIST OF STUDY STAFF

Sponsor:	Zydus Discovery DMCC
Medical Monitor	
Sponsors' Medical Expert's	
Serious Adverse Event Reporting:	
Contract Research Organization	

PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2, Prospective, Multicenter, Double-blind, Randomized Study of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg Versus Placebo in Patients with Nonalcoholic Fatty Liver Disease and/or Nonalcoholic Steatohepatitis
Protocol Number:	[redacted]
IND Number:	IND 128791
Development Phase:	Phase 2
Sponsor:	Zydus Discovery DMCC
Clinical Research Organization:	[redacted]
Study Objectives:	**Primary Objective** • To investigate the effect of a 16-week treatment regimen of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg on serum alanine aminotransferase (ALT) levels in patients with nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH). **Secondary Objectives** • To assess the effect of a 16-week treatment regimen of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg on the following parameters in patients with NAFLD and/or NASH: 1 Change in liver fat content at Week 16 as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF). 2 Proportion of patients who sustain a decrease in serum ALT levels observed at Week 4, Week 8 and Week 12 and Week 16 of therapy. 3 Changes in serum-based predictors of liver injury and fibrosis (cytokeratin-18 [CK-18], Enhanced liver fibrosis [ELF] and aspartate aminotransferase-to-platelet ratio index [APRI]), at Week 8 and Week 16 of therapy. 4 Pharmacokinetics of Saroglitazar Magnesium following first dose and last dose. 5 Quality of life (QoL). 6 Safety and tolerability of repeat dosing of 1 mg, 2 mg or 4 mg Saroglitazar Magnesium. **Exploratory Objectives** • To explore the effect of a 16-week treatment regimen of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg on the following parameters in patients with NAFLD: 1. Liver stiffness as measured by transient elastography/FibroScan®. 2. Continuous attenuation parameter (CAP) as measured by transient elastography/FibroScan. 3. Fasting lipid and lipoprotein profiles (lipoprofiles) at Week 4, Week 8, Week 12 and Week 16 of treatment. 4. Insulin resistance and glycemic control at Week 8 and Week 16 of treatment.

Study Design:	This is a randomized, double-blind, placebo-controlled study in up to 104 patients with a diagnosis of NAFLD and/or NASH. The study will be conducted over a period of up to 22 weeks and will include an optional Pre-screening , a Screening (Days -35 to -7), a 16-week Treatment Phase following randomization on Day 1 to either Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo orally once daily in the morning before breakfast. **Pre-screening** The study sites may identify potential subjects by conducting a laboratory evaluation of the ALT levels. This optional pre-screening can be conducted before the actual study screening. A subject with an ALT ≥50 U/L may be considered for the actual study screening. Also, along with the evaluation of the ALT levels, in those potential subjects who do not have a documented diagnosis of NAFLD through any imaging method, an optional abdominal ultrasound may be performed during the pre-screening. The evaluation of the ALT levels during the pre-screening will be done at the local laboratory, whereas the laboratory evaluations during the Screening and the Treatment Phase will be done at the central laboratory. An informed consent has to be obtained from the potential subjects before any pre-screening evaluations. **Screening** Visit 1 (Day -35): Patient eligibility for participation in the study will be assessed. Medical history will be obtained; physical examination, electrocardiogram (ECG) and laboratory evaluations (including serology, clinical chemistry, hematology, liver enzymes and urinalysis) will be performed. Female patients will undergo a serum pregnancy test. Serum ALT must be ≥50 U/L to proceed further in the study. In addition, Investigator will instruct the patient to maintain their current diet and physical activity at each visit. Visit 2 (Day -14 to -7): Liver enzymes (AST, ALT, ALP and total bilirubin (TB) will be re-measured approximately 3 weeks from Day -35 to determine eligibility. Elevated ALT ≥50 U/L on 2 occasions in the Screening is necessary for study entry. The variance in the levels of the repeat measures of serum ALT and total bilirubin (TB) at Day -14 (Visit 2) must be ≤30%, compared to the Day -35 (Visit 1) levels to be eligible for study entry. The liver function test values at Day -14 to -7 (Visit 2) will be considered as baseline for the efficacy assessment. **Randomization & Treatment Phase** The Randomization & Treatment Phase will include 5 additional outpatient visits over a period of 16 weeks including the randomization visit. Efficacy assessments will be conducted on these 5 visits by measuring liver enzymes (AST, ALT, ALP and TB, CK-18 fragments, ELF, fasting glucose, serum insulin levels, lipoprofile, homeostasis model assessment (insulin resistance [HOMA-IR]) and homeostasis model assessment (β cell function [HOMA-β], liver stiffness and CAP by transient elastography/FibroScan, liver fat content with MRI-PDFF and QoL. In addition, safety assessments will be conducted and there will be no clinically significant changes in dietary, physical activity or alcohol consumption. Visit 3 (Day 1): Patients will be randomly assigned to receive Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo orally once daily, starting on Day 1 of a 16-week outpatient treatment period. Patients will commence with a once daily oral dosing

	regimen. Visits 4, 5 and 6: Patients will visit the study site at Week 4 (Visit 4), Week 8 (Visit 5) and Week 12 (Visit 6) for clinical assessment, dispensation and reconciliation of study drug, measurements of efficacy endpoints and assessment of adverse events (AEs). End-of-Treatment Visit (Visit 7): An End-of-treatment Visit will occur at Week 16 for clinical assessment, reconciliation of study drug, and measurements of efficacy and AEs. Telephone follow-up will occur 7 days (± 3 days) after the End-of-treatment Visit for safety monitoring.
Study Drug:	Study drugs include oral tablets containing 1 mg, 2 mg or 4 mg Saroglitazar Magnesium and matching placebo tablets. Patients will be randomly assigned to receive Saroglitazar Magnesium 1 mg, 2 mg or 4 mg or matching placebo once daily in the morning before breakfast for 16 Weeks.
Number of Patients:	One-hundred-four (104) patients are planned for enrollment. Patients will be randomly assigned to receive active drug (Saroglitazar Magnesium 1 mg, 2 mg or 4 mg) or placebo in a 1:1:1:1 ratio. Approximately eight patients in each group are planned for pharmacokinetic assessments therefore a total of approximately 32 patients will be included in the pharmacokinetic study.
Study Population:	Patients with NAFLD and/or NASH who have elevated ALT (defined as ≥50 U/L at the Screening Visits) will be eligible for the study if they meet all of the inclusion criteria and none of the exclusion criteria. **Inclusion Criteria** 1. Males or females, 18 to 75 years of age, with body mass index (BMI) ≥25 kg/m^2. 2. Documented diagnosis of NAFLD established either by imaging (ultrasound, CT scan or MRI) or liver biopsy showing NASH or simple steatosis, within the 24 months preceding Visit 1. The diagnosis of NAFLD is made according to the American Association for the Study of Liver Diseases (AASLD) criteria (Chalasani et al. Hepatology 2012; 55:2005-2023). 3. ALT level of ≥50 U/L at Visit 1 and Visit 2 with ≤30% variance between the levels at Visit 1 and Visit 2. 4. Patient's demonstration of understanding of study requirements and treatment procedures, willingness to comply with all protocol-required evaluations; provision of written informed consent before any study specific tests or procedures are performed. **Exclusion Criteria** 1. Consumption of >3 units of alcohol per day (>21 units per week) if male and >2 units of alcohol per day (>14 units per week) if female for at least 3 consecutive months in the 5 years preceding Visit 1 (Note: 1 unit = 12 ounces of beer, 4 ounces of wine or 1 ounce of spirits/hard liquor). 2. Presence of alternative causes of fatty liver, including: a. Weight change >5% within the 3 months preceding Visit 1 b. Total parenteral nutrition, starvation or protein-calorie malnutrition

	within the 90 days preceding Visit 1. c. Use of drugs associated with NAFLD for more than 12 consecutive weeks in the 1 year before Visit 1, including amiodarone, tamoxifen, methotrexate, systemic glucocorticoids, anabolic steroids, tetracycline, estrogens in doses higher than used in oral contraceptives, vitamin A, L asparaginase, valproate, chloroquine or antiretroviral drugs 3. Initiation of vitamin E at doses >100 IU/day, or multivitamins containing >100 IU/day of vitamin E in the 3 months preceding Visit 1. 4. Use of drugs with potential effect on NASH such as ursodeoxycholic acid, S-adenosylmethionine (SAM-e), betaine, pentoxifylline, obeticholic acid or milk thistle in the 3 months prior to Visit 1. 5. Changing doses of statins (simvastatin, pitavastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin) or fibrates (clofibrate, fenofibrate) in the 3 months preceding Visit 1. 6. Use of thiazolidinediones (pioglitazone, rosiglitazone). 7. Use of drugs that are known CYP2C8 inhibitors/substrate (please refer to Section 5.8.1.1 Excluded Concomitant Medications). 8. History of bowel surgery (gastrointestinal (bariatric) surgery or undergoing evaluation for bariatric surgery for obesity, extensive small-bowel resection or orthotopic liver transplant (OLT) or listed for OLT. 9. History of other chronic liver disease (chronic hepatitis C, (HCV) infection, irrespective of their mRNA HCV assay status or active hepatitis B infection, (i.e., serum positive for hepatitis B surface antigen) or autoimmune hepatitis, cholestatic and metabolic liver diseases) or hemochromatosis 10. Patient has known cirrhosis, either based on clinical criteria or liver histology. 11. Patient with INR >1.3. 12. Type 1 diabetes mellitus. 13. Poorly controlled type 2 diabetes mellitus, i.e., glycosylated hemoglobin (HbA1c) >9%. 14. Unstable cardiovascular disease, including: a. unstable angina, (i.e., new or worsening symptoms of coronary heart disease within the 3 months preceding Visit 1), acute coronary syndrome within the 6 months preceding Visit 1, acute myocardial infarction within the 3 months preceding Visit 1 or heart failure of New York Heart Association class (III – IV) or worsening congestive heart failure, or coronary artery intervention, within the 6 months preceding Visit 1 b. history of (within 3 months preceding Visit 1) or current unstable cardiac dysrhythmias c. uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg and/or diastolic BP >100 mmHg)

	d. stroke or transient ischemic attack within the 6 months preceding Visit 1. 15. History of myopathies or evidence of active muscle disease. 16. History of malignancy in the 5 years preceding Visit 1 and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer. 17. Any of the following laboratory values: a. Hemoglobin <9 g/dL b. White blood cell count $<2.5 \times 10^3/\mu L$ c. Neutrophil count $<1.5 \times 10^3/\mu L$ d. Platelets $<100 \times 10^3/\mu L$ e. Total Serum bilirubin >1.5 mg/dL (except in patient with known Gilbert bilirubin where TB up to 2.5 mg/dL is allowed), if it is <1.5 mg/dL at screening and >30% variance in the levels at Visit 1 and Visit 2 f. Albumin <3.2 g/dL g. Serum creatinine >1.5 mg/dL h. Serum ALT or AST >250 U/L at Visit 1 or Visit 2. 18. Contraindications to Saroglitazar Magnesium or has any conditions affecting the ability to evaluate the effects of Saroglitazar Magnesium. 19. Known allergy, sensitivity or intolerance to the study drug, placebo or formulation ingredients. 20. Participation in any other therapeutic clinical study within the 3 months preceding Visit 1, including participation in any other NAFLD/NASH clinical trials. 21. History of bladder disease and/or hematuria or has current hematuria except due to a urinary tract infection. 22. Illicit substance abuse within the 12 months preceding Visit 1. 23. Pregnancy-related exclusions, including: a. Pregnant/lactating female (including a positive serum pregnancy test at Visit 1) b. A male patient has to use a condom with spermicide, and the female partner of the male patient has to use an intrauterine device OR a diaphragm with spermicide OR oral contraceptive pills. c. If a male patient has undergone a vasectomy, the female partner does not have to use any contraception. d. A female patient has to use either an intrauterine device OR a diaphragm with spermicide OR oral contraceptive pills. The male partner of the female patient has to use a condom with spermicide. e. If the female patient is surgically sterilized for at least the 6 months preceding Visit 1 or postmenopausal, defined as at least 12 months with no menses and without an alternative cause, the male partner of the

	female patient does not have to use any contraception. 24. History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study (such as poorly controlled psychiatric disease, HIV, coronary artery disease or active gastrointestinal conditions that might interfere with drug absorption).
Criteria for Evaluation:	**Primary Efficacy Endpoint** Percentage change from baseline in serum ALT levels at Week 16 in the Saroglitazar Magnesium groups as compared to the placebo group. **Secondary Efficacy Endpoints** 1 Change in liver fat at Week 16 as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF). 2 Percentage change from baseline and absolute change from baseline in serum ALT levels at Week 4, Week 8 and Week 12 of treatment in the Saroglitazar Magnesium groups as compared to the placebo group. 3 Proportion of patients who sustain a decrease in ALT observed at Week 4, Week 8 Week 12 and Week 16 in the Saroglitazar Magnesium groups as compared to the placebo group. 4 Proportions of patients with ≥25% and ≥50% reduction from baseline in ALT levels at Week 4, Week 8, Week 12 and Week 16 in the Saroglitazar Magnesium groups as compared to the placebo group. 5 Percentage change from baseline and absolute change from baseline in CK-18 fragments, ELF score and APRI at Week 8, and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group. 6 Absolute change from baseline in AST/ALT ratio at Week 4, Week 8, Week 12 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group. 7 Pharmacokinetics of Saroglitazar Magnesium following first dose and last dose in patients with NAFLD/NASH. 8 Absolute change in the Short-Form 36 Health Survey Version 2.0 (SF 36) 8 domain scores and 2 component scores (separate analyses) change from baseline in QoL scores at Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group. **Exploratory Efficacy Endpoints** 1. Changes in liver stiffness/CAP as measured by transient elastography/FibroScan in the Saroglitazar Magnesium groups as compared to the placebo group. 2. Absolute changes in fasting lipid and lipoprofiles at Week 4, Week 8, Week 12 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group. 3. Absolute changes in insulin resistance and glycemic control (adiponectin, fasting insulin, fasting blood glucose, C peptide, HOMA-IR and HOMA-ß, free fatty acids) at Week 8 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group. Absolute change in HbA1c will be assessed at Week 16. **Safety Endpoints** • Frequency and severity of AEs and serious AEs.

	• Clinical laboratory testing (hematology, clinical chemistry and urinalysis). • Twelve-lead electrocardiogram (ECG). • Vital signs.
Statistical Methods:	Sample Size: The endpoint that determines the sample size for this trial is the percentage change from baseline to Week 16 in serum ALT levels. Descriptive statistics was calculated for the percentage change from baseline to Week 12 in serum ALT levels from a clinical study on Saroglitazar Magnesium in NASH patients [redacted] Sample size is based on a 1-sided t-test (2 independent samples) at the 5% significance level for the percentage change from baseline between Saroglitazar Magnesium 4 mg and placebo at Week 12 (a 1-sided test ignores the small probability of a significant result in the "wrong" direction [i.e., superiority of placebo over Saroglitazar Magnesium]. As this is a proof-of-concept [PoC] study, this approach is acceptable). A sample size of 23 patients in each arm will provide 95% power to detect a difference in mean of 25% of ALT (U/L) levels between Saroglitazar Magnesium (1 mg, 2 mg, 4 mg) and placebo assuming a common standard deviation of approximately 25%. Therefore, allowing for 10% attrition between randomization and inclusion in the full analysis set (FAS), a total of 104 patients will be required in the study (26 randomized to placebo and 26 patients randomized to each Saroglitazar Magnesium arm, i.e. 1 mg, 2 mg or 4 mg). Efficacy Analysis: All efficacy analyses will be based primarily on the FAS, and analyses based on the Per Protocol (PP) analysis set will be secondary to this, as required. The FAS will consist of all patients who have been randomized, taken at least 1 dose of the study treatment and have provided efficacy data for at least 1 endpoint. The PP analysis set will consist of all patients in the FAS who have additionally completed the double-blind treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome. The PP analysis set will be defined prior to unblinding the study. Primary Efficacy Analysis: The primary analysis for the primary efficacy endpoint will be based on the FAS. The primary efficacy endpoint in this study is percentage change from baseline to Week 16 in serum ALT levels and will be analyzed using an analysis of covariance (ANCOVA) model with treatment as factor and baseline ALT levels as covariate. The comparison of interest is Saroglitazar Magnesium 1 mg, 2 mg or 4 mg versus placebo at Week 16. Least squares (LS) means for each treatment group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 90% confidence intervals will be provided. These will be derived from the calculation of Type III LS Means from ANCOVA and presented. One-tailed P value will also be presented to test the alternative hypothesis that Saroglitazar Magnesium is superior to placebo. Missing values will be imputed by carrying forward the last observation value after baseline.

	Secondary analyses (of the primary endpoint) will be analyzed using a similar analysis in the PP Analysis Set. Residual analysis will be used to check assumptions for the ANCOVA model. Should any of the assumptions of the analysis method not be adequately met, an alternative procedure will be used and fully documented. Secondary Efficacy Analysis: Due to this being a proof-of-concept study, no adjustment of any P values will be made to account for inflation of the Type 1 error rate arising from testing multiple endpoints, or testing the same endpoint at different times. Each secondary efficacy endpoint will be summarized by treatment group at each time point, as appropriate. Endpoints such as percentage change from baseline to Week 4, Week 8 and Week 12 in serum ALT levels; absolute changes from baseline in AST/ALT ratio and ELF score; absolute and percentage changes from baseline in CK-18 and APRI after Week 8 and Week 16; and change in liver fat at Week 16 will be analyzed using ANCOVA model with treatment as factor and baseline level as covariate. Analysis will be presented similar to primary analysis. These analyses will also be supported by simple summaries (n, mean, standard deviation, median, minimum and maximum) at each visit, without covariate adjustment. Proportions of patients with percentage reductions of ≥25% and ≥50% from baseline in ALT levels at Week 4, Week 8, Week 12 and Week 16 will be analyzed using logistic regression including terms for baseline ALT levels and treatment. Endpoints based on proportion of patients will be summarized. For the categorical data, descriptive summary statistics will be, summarizing the number and percentage of patients in each category at each visit. Descriptive statistics will be provided for each pharmacokinetic parameter. Safety Analysis: Safety analyses will be based on the Safety Analysis Set which will consist of all patients who are known to have received at least 1 dose of study treatment, with patients grouped according to the actual treatment received. Demographics and other safety endpoints (AEs, clinical laboratory testing, ECG and vital signs) will be summarized by using the following descriptive statistics: N, mean, median, standard deviation, minimum and maximum for continuous variables, and patient counts and percentages for categorical variables. Safety summaries will be presented by treatment group for all treated patients. Exploratory Analysis: The individual values of the exploratory endpoints will be listed and summary statistics will be calculated for each treatment group. The exploratory analyses will be based primarily on the FAS, and analyses based on the PP Analysis Set will be secondary to this.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
apo A	Apolipoprotein A
apo B	Apolipoprotein B
APRI	Aspartate aminotransferase-to-platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BL	Baseline
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CAP	Continuous attenuation parameter
CK-18	Cytokeratin-18
CTCAE	Common Terminology Criteria for Adverse Event
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
DILI	Drug-induced liver injury
DPP-4	Dipeptidyl peptidase 4
ECG	Electrocardiogram
EDC	Electronic data capture
ELF	Enhanced liver fibrosis
FA	Fatty acid
FAS	Full analysis set
FDA	Food and Drug Administration
FFA	Free fatty acids

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HepB	Hepatitis B
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic model assessment – insulin resistance
HOMA-ß	Homeostatic model assessment – β-cell function
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LFT	Liver function test
LPL	Lipoprotein lipase
LS	Least squares
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	Magnetic resonance imaging-derived proton density-fat fraction
NAFLD	Nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
OLT	Orthotropic liver transplant
OTC	Over-the-counter
PI	Principal Investigator
PP	Per protocol

PPAR	Peroxisome proliferator-activated receptor
PoC	Proof-of-concept
PT	Prothrombin time
QoL	Quality of life
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SF-36	Short-Form 36 Health Survey Version 2.0 (SF-36)
TEAE(s)	Treatment-emergent adverse event(s)
TG	triglycerides
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
WBC	White blood cell

1. INTRODUCTION

1.1 Background

1.1.1 Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease (Angulo, 2002; Wieckowska and Feldstein, 2005). The severity of NAFLD ranges from relatively benign simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by hepatocellular injury, inflammation and risk of progression to cirrhosis with complications of portal hypertension, liver failure and hepatocellular carcinoma (Matteoni et al., 1999; McCullough, 2004; Brunt and Tiniakos, 2005). Nonalcoholic steatohepatitis is considered a hepatic manifestation of the metabolic syndrome. In many patients, insulin resistance underlies the development of the metabolic syndrome; consequently, NASH is highly prevalent among patients with type 2 diabetes. Currently, obesity and associated type 2 diabetes have reached epidemic proportions and are considered burgeoning public health problems (Hu, 2011).

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.

Peroxisome proliferator-activated receptor (PPAR) agonists are known to lower high blood triglyceride levels (PPARα agonists) and improve insulin resistance (PPARγ agonists), and therefore offer a potential treatment for NAFLD or NASH.

1.1.2 Saroglitazar Magnesium

Saroglitazar, [redacted] is a novel peroxisome PPAR agonist with dual PPAR agonistic properties – it is a potent and predominant PPARα agonist with moderate PPARγ agonistic activity.

PPARs are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. The pharmacological effects of Saroglitazar Magnesium were extensively evaluated in various preclinical models. Saroglitazar Magnesium showed both

antidyslipidemic and antidiabetic effects, mainly mediated via activation of PPARα and PPARγ, respectively.

PPARα activation by Saroglitazar Magnesium increases the hepatic oxidation of fatty acids (FA) and reduces the synthesis and secretion of triglycerides (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 low-density lipoprotein (LDL) cholesterol. PPARα activation by Saroglitazar Magnesium also induces an increase in the synthesis of apolipoproteins, A-I, A-II and high-density lipoprotein (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 postabsorptive 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.

Saroglitazar Magnesium has been the first glitazar granted marketing authorization in India and is indicated for treatment of diabetic dyslipidemia. The drug was developed with an expectation to achieve optimum antidyslipidemic and antihyperglycemic effects, while avoiding adverse events (AEs) such as peripheral edema, weight gain, cardiovascular events, renal and/or liver toxicity, etc., which are commonly seen with other dual PPAR or PPARα agonists.

1.2 Rationale for the Clinical Study

Saroglitazar Magnesium is known to safely and effectively improve dyslipidemia by reducing TG, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, non-high-density lipoprotein (non-HDL) cholesterol and increasing HDL cholesterol. In addition, Saroglitazar

Magnesium can improve glycemic indices in diabetic patients by reducing fasting serum glucose and glycosylated hemoglobin. Considering the association between insulin resistance, dyslipidemia and the development of NASH, Saroglitazar Magnesium could potentially benefit patients with NAFLD including those with NASH. Therefore, the purpose of the present proof-of-concept (PoC) study is to examine the efficacy of Saroglitazar Magnesium in improving various measures of hepatic inflammation and injury associated with NAFLD, with improvement in ALT being the primary endpoint.

1.3 Risk-Benefit Assessment

Considering the results of earlier studies with Saroglitazar Magnesium, patients could benefit from the Saroglitazar Magnesium 1 mg, 2 mg or 4 mg treatment because of the drug's ability to improve dyslipidemia and glycemic indices. It is possible that treatment with Saroglitazar Magnesium may be associated with a reduction in elevated liver enzyme levels and/or liver elasticity. Controlled phase 3 clinical studies in patients with dyslipidemia with Saroglitazar Magnesium 2 mg or 4 mg over periods of 12 or 24 weeks had a very favorable safety profile. Therefore, the available information suggests that the present study has a favorable risk-benefit ratio.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To investigate the effect of a 16-week treatment regimen of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg on serum alanine aminotransferase (ALT) levels in patients with nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH).

2.2 Secondary Objectives

- To assess the effect of a 16-week treatment regimen of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg on the following parameters in patients with NAFLD and/or NASH:
    1 Change in liver fat content at Week 16 as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF).
    2 Proportion of patients who sustain a decrease in serum ALT levels observed at Week 4, Week 8, Week 12 and Week 16 of therapy.
    3 Changes in serum-based predictors of liver injury and fibrosis [cytokeratin-18 (CK-18), Enhanced liver fibrosis (ELF) and aspartate aminotransferase-to-platelet ratio index (APRI)], at Week 8 and Week 16 of therapy.
    4 Pharmacokinetics of Saroglitazar Magnesium following first dose and last dose.
    5 Quality of life (QoL).
    6 Safety and tolerability of repeat dosing of 1 mg, 2 mg or 4 mg Saroglitazar Magnesium.

2.3 Exploratory Objectives

- To explore the effect of a 16-week treatment regimen of Saroglitazar Magnesium 1 mg, 2 mg or 4 mg on the following parameters in patients with NAFLD and/or NASH:
    1. Liver stiffness as measured by transient elastography/FibroScan®.
    2. Continuous attenuation parameter (CAP) as measured by transient elastography/FibroScan.
    3. Fasting lipid and lipoprotein profiles (lipoprofiles) at Week 4, Week 8, Week 12 and Week 16 of treatment.
    4. Insulin resistance and glycemic control at Week 8 and Week 16 of treatment.

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a randomized, double-blind, placebo-controlled study in up to 104 patients with a diagnosis of NAFLD and/or NASH. The study will be conducted over a period of up to 22 weeks and will include an optional Pre-screening, a 5-week Screening and a 16-week Treatment Phase following randomization on Day 1 to either Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo orally once daily in the morning before breakfast. Please refer to the Schedule of Assessments (Table 4) for a detailed schedule of procedures performed on each study day/visit.

Pre-screening

The study sites may identify potential subjects by conducting a laboratory evaluation of the ALT levels. This optional pre-screening can be conducted before the actual study screening. A subject with an ALT ≥50 U/L may be considered for the actual study screening.

Also, along with the evaluation of the ALT levels, in those potential subjects who do not have a documented diagnosis of NAFLD through any imaging method, an optional abdominal ultrasound may be performed during the pre-screening.

The evaluation of the ALT levels during the pre-screening will be done at the local laboratory, whereas the laboratory evaluations during the Screening and the Treatment Phase will be done at the central laboratory.

An informed consent has to be obtained from the potential subjects before any pre-screening evaluations.

Screening

Visit 1 (Day -35): Patient eligibility for participation in the study will be assessed. Medical history will be obtained, physical examination, electrocardiogram (ECG) and laboratory evaluations (including serology, clinical chemistry, hematology, liver enzymes and urinalysis) will be performed. Female patients will undergo a serum pregnancy test. Serum ALT must be ≥50 U/L to proceed further in the study. In addition, PI will instruct the patient to maintain his or her current diet and physical activity at each visit.

Visit 2 (Day -14 to -7): Liver enzymes (AST, ALT, ALP and total bilirubin [TB]) will be re-measured approximately 3 weeks from Day -35 to determine eligibility. Elevated ALT ≥50 U/L on 2 occasions in the Screening is necessary for study entry. The variance in the levels of

the repeat measures of serum ALT and TB at Day -14 (Visit 2) must be ≤30%, compared to the Day -35 (Visit 1) levels to be eligible for study entry.

(Calculation of the variance and round of laboratory values will be done as following;

Rounding up of the values will be done according to the following method:

For e.g. 31.1, 31.2, 31.3, 31.4 will be rounded off to 31.

31.5, 31.6, 31.7, 31.8, 31.9 will be rounded off to 32.

0.21, 0.22, 0.23, 0.24 will be rounded off to 0.2

0.25, 0.26, 0.27, 0.28, 0.29 will be rounded off to 0.3

1. An example with ALT values

If the ALT values of subject xx at visit 1 is 73 U/L

Calculate the 30% of 73 which is 21.9

+ 30% is 73 + 21.9 which is 94.9 U/L (rounded off to 95)

- 30% is 73 – 21.9 which is 51.1 U/L (rounded off to 51)

The ALT value of the same subject at visit 2 has to be not ≤51U/L and not ≥95 U/L. However, please keep in mind that the ALT at visit 2 also needs to be ≥50 U/L).

The liver function test (LFT) values at Day -14 to -7 (Visit 2) will be considered as baseline for the efficacy assessment.

Randomization & Treatment Phase

The Randomization & Treatment Phase will include 5 additional outpatient visits over a period of 16 weeks including the randomization visit. Efficacy assessments will be conducted on these 5 visits by measuring liver enzymes, CK-18 fragments, ELF, fasting glucose, serum insulin levels, lipoprofile, homeostasis model assessment (insulin resistance [HOMA-IR]) and homeostasis model assessment (β cell function [HOMA-β], liver stiffness and CAP by transient elastography/FibroScan, liver fat content with MRI-PDFF and QoL. In addition, safety assessments will be conducted and there will be no clinically significant changes in dietary, physical activity or alcohol consumption.

Visit 3 (Day 1): Patients will be randomly assigned to receive Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo orally once daily, starting on Day 1 of a 16-week outpatient treatment period. Patients will commence with a once daily oral dosing regimen.

Visits 4, 5 and 6: Patients will visit the study site at Week 4 (Visit 4), Week 8 (Visit 5) and Week 12 (Visit 6) for clinical assessment, dispensation and reconciliation of study drug, measurements of efficacy endpoints and assessment of AEs.

End-of-Treatment Visit (Visit 7): An End-of-treatment Visit will occur at Week 16 for clinical assessment, reconciliation of study drug and measurements of efficacy and AEs.

Telephone follow-up will occur 7 days (± 3 days) after the End-of-treatment Visit for safety monitoring.

3.2 Endpoints

The study involves primary and secondary efficacy endpoints and safety assessments. The specific endpoints are listed below.

3.2.1 Primary Efficacy Endpoint

- Percentage change from baseline in serum ALT levels at Week 16 in the Saroglitazar Magnesium groups as compared to the placebo group

3.2.2 Secondary Efficacy Endpoints

1 Change in liver fat at Week 16 as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF).

2 Percentage change from baseline and absolute change from baseline in serum ALT levels at Week 4, Week 8 and Week 12 of treatment in the Saroglitazar Magnesium groups as compared to the placebo group.

3 Proportion of patients who sustain a decrease in ALT observed at Week 4, Week 8, Week 12 and Week 16 in the Saroglitazar Magnesium groups as compared to the placebo group.

4 Proportions of patients with ≥25% and ≥50% reduction from baseline in ALT levels at Week 4, Week 8, Week 12 and Week 16 in the Saroglitazar Magnesium groups as compared to the placebo group.

5 Percentage change from baseline and absolute change from baseline in CK-18 fragments, ELF score and APRI at Week 8 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group.

6 Absolute change from baseline in AST/ALT ratio at Week 4, Week 8, Week 12 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group.

7 Pharmacokinetics of Saroglitazar Magnesium following first dose and last dose in patients with NAFLD/NASH.

8 Absolute change from baseline in the Short-Form 36 Health Survey Version 2.0 (SF 36) 8 domain scores and 2 component scores (separate analyses) change from baseline in QoL scores at Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group.

3.2.3 Exploratory Efficacy Endpoints

1. Changes in liver stiffness/CAP as measured by transient elastography/FibroScan in the Saroglitazar Magnesium groups as compared to the placebo group.
2. Absolute changes in fasting lipid and lipoprofiles at Week 4, Week 8, Weeks 12 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group.
3. Absolute changes in insulin resistance and glycemic control (adiponectin, fasting insulin, fasting blood glucose, C peptide, HOMA-IR and HOMA-ß, free fatty acids) at Week 8 and Week 16 after treatment in the Saroglitazar Magnesium groups as compared to the placebo group. Absolute change in HbA1c will be assessed at Week 16.

3.2.4 Safety Endpoints

- Frequency and severity of AEs and serious AEs
- Clinical laboratory testing (hematology, clinical chemistry and urinalysis)
- Twelve-lead ECG
- Vital signs.

3.3 Justification of the Study Design

The present study was designed in accordance with the recommendations set out by the American Association for the Study of Liver Diseases, the American Gastroenterological

Association and the American College of Gastroenterology Multisociety Practice Guidelines, including "Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis" authored by Sanyal et al and published by the National Institute of Health (Sanyal et al., 2011).

Recommendations regarding the diagnosis of NAFLD, disease activity and disease staging are incorporated into the inclusion/exclusion criteria of the study and the inclusion and exclusion criteria is designed to accurately identify patients with NAFLD. During the Treatment Phase, patients will be monitored at appropriate intervals for AEs and changes in laboratory parameters.

4. STUDY POPULATION

The study population will consist of patients with NAFLD and/or NASH who have elevated ALT (defined as ≥50 U/L at the Screening Visits). Patients will be eligible for the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1 Number of Patients

One-hundred-four patients will be enrolled in the clinical study according to the inclusion/exclusion criteria outlined below. Patients will be randomly assigned to receive Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo in a 1:1:1:1 ratio.

Total ~32 patients (~8 patients from each treatment arm i.e. Saroglitazar Magnesium 1 mg, 2 mg or 4 mg, and placebo) will participate in pharmacokinetic assessment.

4.2 Inclusion Criteria

Patients who meet the following criteria will be considered eligible to participate in the clinical study:

1. Males or females, 18 to 75 years of age, with body mass index (BMI) ≥25 kg/m^2.
2. Documented diagnosis of NAFLD established either by imaging (ultrasound, CT scan or MRI) or liver biopsy showing NASH or simple steatosis, within the 24 months preceding Visit 1. The diagnosis of NAFLD is made according to the American Association for the Study of Liver Diseases (AASLD) criteria (Chalasani et al. Hepatology 2012; 55:2005-2023).
3. ALT level of ≥50 U/L at Screening Visit 1 and Visit 2 with ≤30% variance in the levels at Visit 1 and Visit 2.
4. Patient's demonstration of understanding of study requirements and treatment procedures, willingness to comply with all protocol-required evaluations; provision of written informed consent before any study specific tests or procedures are performed.

4.3 Exclusion Criteria

1. Consumption of >3 units of alcohol per day (>21 units per week) if male and >2 units of alcohol per day (>14 units per week) if female for at least 3 consecutive months in the 5 years preceding Visit 1 (Note: 1 unit = 12 ounces of beer, 4 ounces of wine or 1 ounce of spirits/hard liquor).

2. Presence of alternative causes of fatty liver, including:
    a. Weight change >5% within the 3 months preceding Visit 1
    b. Total parenteral nutrition, starvation or protein-calorie malnutrition within the 90 days preceding Visit 1
    c. Use of drugs associated with NAFLD for more than 12 consecutive weeks in the 1 year before Screening Visit 1, including amiodarone, tamoxifen, methotrexate, systemic glucocorticoids, anabolic steroids, tetracycline, estrogens in doses higher than used in oral contraceptives, vitamin A, L asparaginase, valproate, chloroquine or antiretroviral drugs.
3. Initiation of vitamin E at doses >100 IU/day, or multivitamins containing >100 IU/day of vitamin E in the 3 months preceding Visit 1.
4. Use of drugs with potential effect on NASH such as ursodeoxycholic acid, S-adenosylmethionine (SAM-e), betaine, pentoxifylline, obeticholic acid or milk thistle in the 3 months prior to Visit 1.
5. Changing doses of statins (simvastatin, pitavastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin) or fibrates (clofibrate, fenofibrate) in the 3 months preceding Visit 1.
6. Use of thiazolidinediones (pioglitazone, rosiglitazone).
7. Use of drugs that are known CYP2C8 inhibitors/substrate (please refer Section 5.8.1.1 Excluded Concomitant Medications).
8. History of bowel surgery (gastrointestinal (bariatric) surgery or undergoing evaluation for bariatric surgery for obesity, extensive small-bowel resection or orthotopic liver transplant (OLT) or listed for OLT.
9. History of other chronic liver disease (chronic hepatitis C, (HCV) infection, irrespective of their mRNA HCV assay status, or active hepatitis B infection, (i.e., serum positive for hepatitis B surface antigen) or autoimmune hepatitis, cholestatic and metabolic liver diseases) or hemochromatosis.
10. Patient has known cirrhosis, either based on clinical criteria or liver histology.
11. Patient with INR >1.3.
12. Type 1 diabetes mellitus.
13. Poorly controlled type 2 diabetes mellitus, i.e., glycosylated hemoglobin (HbA1c) >9%.

14. Unstable cardiovascular disease, including:
    a. unstable angina, (i.e., new or worsening symptoms of coronary heart disease within the 3 months preceding Visit 1), acute coronary syndrome within the 6 months preceding Visit 1, acute myocardial infarction within the 3 months preceding Visit 1 or heart failure of New York Heart Association class (III – IV) or worsening congestive heart failure, or coronary artery intervention, within the 6 months preceding Visit 1
    b. history of (within 3 months preceding Visit 1) or current unstable cardiac dysrhythmias
    c. uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg and/or diastolic BP >100 mmHg)
    d. stroke or transient ischemic attack within the 6 months preceding Visit 1.
15. History of myopathies or evidence of active muscle disease.
16. History of malignancy in the 5 years preceding Visit 1 and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer.
17. Any of the following laboratory values:
    a. Hemoglobin <9 g/dL
    b. White blood cell count $<2.5 \times 10^3/\mu L$
    c. Neutrophil count $<1.5 \times 10^3/\mu L$
    d. Platelets $<100 \times 10^3/\mu L$
    e. Total Serum bilirubin >1.5 mg/dL (except in patient with known Gilbert bilirubin where TB up to 2.5 mg/dL is allowed), if it is <1.5 mg/dL at screening and >30% variance in the levels at Visit 1 and Visit 2.
    f. Albumin <3.2 g/dL
    g. Serum creatinine >1.5 mg/dL
    h. Serum ALT or AST >250 U/L at Visit 1 or Visit 2.
18. Contraindications to Saroglitazar Magnesium or has any conditions affecting the ability to evaluate the effects of Saroglitazar Magnesium.

19. Known allergy, sensitivity or intolerance to the study drug, placebo or formulation ingredients.
20. Participation in any other therapeutic clinical study within the 3 months preceding Visit 1, including participation in any other NAFLD/NASH clinical trials.
21. History of bladder disease and/or hematuria or has current hematuria except due to a urinary tract infection.
22. Illicit substance abuse within the 12 months preceding Visit 1.
23. Pregnancy-related exclusions, including:
    a. Pregnant/lactating female (including a positive serum pregnancy test at Visit 1)
    b. A male patient has to use a condom with spermicide, and the female partner of the male patient has to use an intrauterine device OR a diaphragm with spermicide OR oral contraceptive pills.
    c. If a male patient has undergone a vasectomy, the female partner does not have to use any contraception.
    d. A female patient has to use either an intrauterine device OR a diaphragm with spermicide OR oral contraceptive pills. The male partner of the female patient has to use a condom with spermicide.
    e. If the female patient is surgically sterilized for at least the 6 months preceding Visit 1 or postmenopausal, defined as at least 12 months with no menses and without an alternative cause, the male partner of the female patient does not have to use any contraception.
24. History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study (such as poorly controlled psychiatric disease, HIV, coronary artery disease or active gastrointestinal conditions that might interfere with drug absorption).

4.3.1 Screen Failures

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 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 has to 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 Principal Investigator (PI) (or designee) will document on a screening log the reason for the screening failure.

4.3.2 Patient Withdrawal

Patients may withdraw from the entire study at any time without penalty and for any reason without prejudice to his or her future medical care. Although a patient is not obliged to give his/her reason for withdrawing prematurely, the PI will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the PI for follow-up of AE(s) as detailed in Section 6.1.2.8. Every effort will be made to continue clinical and/or laboratory follow-up, as appropriate, in patients who wish to withdraw from the study drug (active drug or placebo) and reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health. A patient's withdrawal of consent and agreement to undergo a final examination will be documented on the case report form (CRF) and on the PI's copy of the ICF, which will be countersigned and dated by the patient.

As far as possible, all assessments scheduled for End-of-treatment must be performed on all patients who receive the study drug but do not complete the study according to protocol.

4.3.3 Discontinuation of Patients from the Study or Study Drug

A patient may be discontinued from the study for any of the following reasons:

- Occurrence of a deviation/noncompliance with the protocol

- Occurrence of a serious or intolerable AE
- The Sponsor or PI terminates the study (Section 4.5)
- Either the PI or the Sponsor decides that discontinuing the study or discontinuing the patient is in the patient's best interest
- For reasons related to safety as specified in Section 4.4
- The patient is lost to follow-up.

A patient may also be discontinued from study drug/study by the Regulatory Authorities or IRB.

A study completion CRF, which includes the reason for discontinuation, must be completed for all patients who are discontinued from the study. If the patient is discontinued prematurely, the study completion CRF should clearly indicate the reason for discontinuation. If the patient discontinues due to an AE, an AE CRF must be completed. The AE must be followed by medical attention to satisfactory resolution and all study data related to the patient will be reported.

Every effort will be made to continue clinical and laboratory follow-up, as appropriate, in patients who are withdrawn or in whom the study drug is stopped by the PI or per individual stopping rules (Section 4.4).

4.3.4 Patients Lost to Follow-up

Every attempt must be made to have all patients complete the visit schedule. A patient will not be considered lost-to-follow-up unless all efforts to obtain compliance are unsuccessful. Study sites should attempt to contact these patients in order to maintain study visit compliance and all contact attempts should be documented in both the patient's medical records and on the study CRFs. At a minimum, the site should make 2 attempts (at least 3 to 5 days apart and during both business and nonbusiness hours) to contact the patient; once by phone and once by certified mail.

4.4 Stopping Criteria for Individual Patients

The following clinical events warrant discontinuation of study drug; however, the patient will continue to be followed for safety, liver function tests and lipid levels until the event has resolved, i.e., clinical laboratory value(s) has/have returned to baseline or is/are no longer of clinical significance. Discontinuation of study drug will only occur if mandated by safety events as defined below:

- Discontinue any patient with a Common Terminology Criteria for Adverse Event (CTCAE) of grade 3 or higher that is possible or likely drug related and discontinue any patient with a CTCAE of grade 4 regardless of attribution to drug.
- Serious AE (SAE) that may be related to the drug and warrant discontinuation as per discretion of the PI;
- In the opinion of the PI, continuation of study drug poses a health risk to the patient.
- Evidence of drug induced liver injury requiring study drug discontinuation as shown in the algorithm below.
- The second LFT values during the Screening (those obtained at Visit 2) will be considered as baseline for the efficacy assessment.
    - If patients with abnormal baseline liver indices develop elevations of AST or ALT greater than 2 times baseline or total bilirubin greater than 1.5 X baseline values (BL) while on study, testing should be repeated within 48-72 hours. If there are persistent elevations in ALT or AST greater than 2 X baseline or TB greater than 1.5 X baseline values, then close observation (see DILI Guidance for definition, testing and physical examination 2-3 times per week) should be initiated or drug should be discontinued.
    - A decision to discontinue or temporarily interrupt a study drug should be considered based on factors that include how much higher baseline ALT and AST were relative to the upper limit of normal (ULN) and how much the on study ALT and AST levels have increased relative to baseline, in addition to whether there is concomitant elevation of bilirubin or INR.
    - The criteria for discontinuing or temporarily interrupting study drug are as follows:
        - When the baseline values were ≥50 U/L but <5 X ULN, discontinue if ALT or AST increases to >3 X BL
        - Discontinue if ALT or AST increase >2 X BL AND the increase is accompanied by a concomitant TBL increase to >2 X BL OR the INR concomitantly increases by >0.2
        - Discontinue and evaluate any patient with elevations of ALT/AST if sign or symptoms of right upper quadrant pain (RUQ), abdominal pain, anorexia, nausea, vomiting fever, eosinophilia and/or rash are present

- If a patient lives in a remote area, they can be tested locally and the results be communicated to the investigator site promptly.

4.5 Termination of the Clinical Study

If the Investigator, the Sponsor or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. Also, the clinical study may be terminated at the Sponsor's discretion in the absence of such a finding.

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

- The discovery of an unexpected, relevant or unacceptable risk to the patients enrolled in the clinical study;
- More than 3 patients develop a CTCAE of grade 3 or higher in any one category;
- 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 study drugs must be returned to the Sponsor. Any actions of Contract Research Organization [redacted]) required for assessing or maintaining patient safety will continue as required, despite termination of the study by the Sponsor.

4.6 Planned Sample Size

It is planned to enroll 104 patients in the US for this study. See Section 8.6 for a discussion of sample size. Patients will be randomly assigned to receive Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo in a 1:1:1:1 ratio.

Of which total ~32 patients (~8 patients from each treatment arm i.e. Saroglitazar Magnesium 1 mg, 2 mg or 4 mg, and placebo) will participate in pharmacokinetic assessment.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1 Identity of the Study Drugs

The products that will be used in this study are outlined in Table 1.

Table 1 Identity of Study Drugs

Study Drug	Formulation	Strength	Route	Manufacturer
Saroglitazar Magnesium	Tablet	1 mg	Oral	[redacted]
Saroglitazar Magnesium	Tablet	2 mg	Oral	[redacted]
Saroglitazar Magnesium	Tablet	4 mg	Oral	[redacted]
Saroglitazar placebo	Tablet	NA	Oral	[redacted]

NA = not applicable
Data source: Investigator's Brochure

[redacted]

[redacted]

5.2 Supply, Packaging, Labeling and Storage

Study drug will be packaged by the Sponsor according to all local legal requirements. [redacted]

Until dispensed to the patients, the study drug will be stored at room temperature (20°C to 25°C or 68°F to 77°F) in a dry place at the study site or pharmacy that can be securely locked and that is accessible to authorized personnel only. If the IP temperature extends outside the 20-25°C range, a temperature excursion must be documented, and sent to the Sponsor and CRO. 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 go beyond the range of $15\text{-}30^{0}$ C will be consider protocol deviation.

5.3 Dispensing and Administration

The PI or designated study personnel will assign the box with the lowest available randomization ID to the first patient to randomize, followed by the next lowest randomization ID to the second patient to randomize and so on [redacted]. The process will begin again using the next outer carton of IP available. One bottle from each inner carton will be dispensed to cover the 4-week interval between study visits (Schedule of Assessments [Table 4]). Patients will be instructed to store study drug in a dry place at room temperature (20°C to 25°C or 68°F to 77°F).

Patients will take 1 tablet of Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo for a period of 112 days. The tablet should be taken at approximately the same time each day. Specific written instructions will be provided on the label and will include directions to take the tablet.

5.4 Drug Accountability

Receipt and dispensing of study drug must be recorded by an authorized person at the study site. The PI will maintain an accurate record of the receipt of the study drug as shipped by the Sponsor, including the date received. Study drug supply management will be processed and maintained in the CRFs and on Drug Accountability forms, which will be monitored and reconciled by the study monitor assigned to the site. This inventory record must be available for inspection at any time. Copies of this record will be provided to the Sponsor at the conclusion of the study.

The PI will not be allowed to store study drug at any site other than those listed on Form FDA 1572 or Investigator's Agreement or to dispense the study drug from sites not listed on this form. The PI will also agree that study drug will be dispensed by the PI or Sub-investigator named on Form FDA 1572 or Investigator's Agreement, or their qualified designees. The PI, Sub-investigators and qualified designees also agree that study drug will be dispensed only to study patients who have provided written informed consent and have met all entry criteria. Study drug may not be used for any purpose other than that stated in the protocol.

After the study has been completed, the PI must account for all study drug used, unused and partially used. All study drug will be adequately destroyed at the site (per site's SOPs) or returned to the Sponsor (or designee). No study drug will be destroyed or returned until drug accountability has been performed by the study monitor.

5.5 Patient Identification and Randomization

5.5.1 Screening Numbers

Patients will be assigned a unique site-specific (e.g., site number 101, 102, etc.,) and patient number (a 3-digit site identification and 3-digit number, e.g., 101-001, 101-002, etc.) that will be used to identify the patient on all data collection forms from Visit 1 until the end of the Treatment Phase.

5.5.2 Randomization Scheme, Randomization Numbers and Allocation of Patients to Treatment

Block Randomization of patients to treatment (placebo, saroglitazar magnesium 1 mg, 2 mg or 4 mg) will occur in 1:1:1:1 ratio. The block randomization will be generated following biostatistics procedure for generation of randomization lists. Each block will contain investigational medicinal products; Saroglitazar Magnesium 1 mg, 2 mg, 4 mg and placebo. [redacted]

On Day 1 of the Treatment (Visit 3), the first eligible patient will be assigned the lowest available randomization ID. The second eligible patient will receive the next lowest available randomization ID [redacted]

5.5.3 Patient Replacements

If patients fail to complete for reasons unrelated to the safety of the study drug, then replacement patients may be enrolled to ensure that each study arm is adequately filled and approximately 104 patients (approximately 26 per treatment arm) complete the study.

5.6 Compliance

At each treatment period visit, study coordinators will log all study drug dispensed to a study patient and returned to the site by the study patient into the CRF for the purpose of drug supply management and accountability. Although 100% compliance to study drug is desired and should be encouraged throughout the treatment phase, a compliance of ≥80% and ≤120% will be considered as acceptable.

5.7 Blinding and Breaking the Blind

The study will be performed in a double-blind manner. All study drugs will be supplied in identical packages and study drug kits and the tablets will be similar in color, smell, taste and appearance, thereby enabling double-blind conditions.

The study blind should not be broken except in a medical emergency where knowledge of the study drug received would affect the treatment of the emergency.

The blind must only be broken following discussion on a case-by-case basis, at the discretion of the Sponsor/Medical Monitor.

If an emergency unblinding becomes necessary, the PI should notify the Sponsor/Medical Monitor, if possible, before unblinding. If it is determined that unblinding is necessary, an

envelope matching the randomization ID will be opened to reveal the treatment received by the patient. All cases resulting in an unblinding event will be documented and reported to the Medical Monitor and the Sponsor. If the blind is broken, the date, time and reason must be recorded in the patient's CRF and any associated AE report completed.

The overall randomization code will be broken only for reporting purposes. This will occur once all final clinical data have been entered into the database and all data queries have been resolved, and the assignment of patients to the analysis sets has been completed.

5.8 Previous and Concomitant Medications and Other Restrictions

5.8.1 Previous and Concomitant Medications

Any medication the patient takes other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications and any changes in the dosage or regimen of a concomitant medication for the 30 days preceding Visit 1 until the end of the study (i.e., the safety telephone call) must be recorded in the CRF.

5.8.1.1 Excluded Concomitant Medications

Patients are not permitted to take Zileuton, unstable dose of vitamin E or other drugs with potential effect on NAFLD such as ursodeoxycholic acid, S-adenosylmethionine (SAM-e), betaine, pentoxifylline, obeticholic acid or milk thistle. In addition, patients are not permitted to take drugs associated with NAFLD during the study period including amiodarone, tamoxifen, methotrexate, systemic glucocorticoids, anabolic steroids, tetracycline, estrogens in doses higher than used in oral contraceptives, vitamin A, L asparaginase, valproate, chloroquine or antiretroviral drugs. The doses of statins (simvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin) or fibrates (clofibrate, fenofibrate) should remain stable throughout the study period as much as possible. Patients are not permitted to thiazolidinediones (pioglitazone, rosiglitazone), chemotherapy or other investigational medications during the study duration.

The known CYP2C8 inhibitors/substrates are not permitted during the study (Appendix 2: List of Known CYP2C8 Inhibitors/Substrates).

Patients also should not take any non-allowed over-the-counter medications or complementary and/or alternative medications believed to have a potential impact that would affect the ability to evaluate the study data.

5.8.1.2 Permitted Concomitant Medications

With the exception of excluded concomitant medications, other medications that patients have been taking at stable dosages for at least 3 months preceding Visit 1, i.e., statins and drugs for glycemic control, will be permitted as concomitant medications, including antidiabetic drugs such as metformin, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors and insulin. To the extent possible, patients should continue with their current regimen of medication without any change throughout the study.

Allowed over-the-counter medications include acetaminophen (maximum 1 gram/day), ibuprofen (maximum 800 mg/day) or naproxen (maximum 440 mg/day) or antacids such as H2 receptor blockers or proton-pump inhibitors for shorter duration as per investigator discretion.

The PI should be alerted if, during the course of the study, a patient requires a new medicine or therapy or a change to an established dosing regimen. All medications that target NAFLD or NASH, or have been suggested to target the underlying causes of NAFLD or NASH, should be reviewed and agreed on by the PI, Medical Monitor and Sponsor before being taken by the patient.

5.8.2 Other Restrictions

5.8.2.1 Alcohol

Patients are encouraged to stop alcohol consumption entirely during the trial. They are not permitted to consume >1 unit of alcohol per day (>7 units per week) during the study. Alcohol consumption will be recorded throughout the study period.

5.8.2.2 Diet and Exercise

Patients must maintain lifestyle modifications, including diet and exercise, previously undertaken according to AASLD guidelines for the duration of the study. Patients should make no major changes in the type or amount of exercise in which they partake during the study.

5.9 Overdose and Drug Interaction

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

6. VARIABLES AND METHODS OF ASSESSMENT

6.1 Safety Variables

There will be a designated safety officer for data and safety monitoring. The safety officer will be an experienced hepatologist with no direct involvement with the study (Please refer Section 7.2 Data Monitoring Committee).

6.1.1 Medical History, Demographic and Other Baseline Information

The medical history comprises:

- General medical history
- Medication history
- Reproductive history.

The following demographic information will be recorded:

- Gender
- Age
- Ethnic origin (Hispanic/Latino or not Hispanic/not Latino)
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American)
- Height, without shoes
- Body weight, without shoes
- Body mass index.

Other baseline characteristics will be recorded as follows:

- History of drug abuse
- History of alcohol abuse
- Smoking history
- History of caffeine use (or other stimulating beverages)
- Diet
- History of blood or plasma donation.

6.1.2 Adverse Events

Adverse event reporting will begin after the informed consent has been signed and will continue until end of the study (i.e., the safety telephone call). The Common Terminology Criteria for Adverse Event (CTCAE) (Version 4.03 or higher) system will be used for reporting and grading AEs.

6.1.2.1 Definitions

An AE is any unfavorable or unintended sign, symptom or disease temporally associated with the use of study drug whether or not considered related to study drug. Adverse events may include:

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

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

6.1.2.2 Serious Adverse Events

Serious Adverse Events

An SAE is an event that:

- Results in death
- Is an immediate threat to life
- Requires hospitalization, or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Is a congenital anomaly or birth defect

Serious AEs also include events that are medically significant in the PI's judgment, including medically significant laboratory abnormalities, such as those that warrant stopping study drug for individual patients as specified in Section 4.4 of the protocol. In general, medically significant events require medical/surgical intervention to prevent one of the outcomes listed above.

6.1.2.3 Treatment-emergent Adverse Events

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

6.1.2.4 Collection of Adverse Events

It is the responsibility of the PI to collect all AEs (both serious and nonserious) derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings, e.g., "How have you felt since I last saw you?"

6.1.2.5 Assessment of Adverse Events

Each AE will be assessed by the PI with regard to the following categories:

Severity

The PI 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 CRF. Severity will be assessed according to the following scale:

Mild: Event is usually transient and easily tolerated, requiring no special treatment and causing no disruption of the 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 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 CRF.

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 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
- Unknown.

6.1.2.6 Recording Adverse Events

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

6.1.2.7 Reporting Serious Adverse Events

The PI must report any SAEs Clinical Studies Safety Center within 24 hours of becoming aware of the event.

When calling to report an SAE, state that you are reporting an SAE and give the PI's name, your name, the telephone number where you can be reached and the protocol number and title.

The PI and the Sponsor (or Sponsor's designated agent) will review each SAE report and the Sponsor will evaluate the seriousness and the causal relationship of the event to study drug. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics). Based on the PI and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

All SAEs will be recorded from signing of informed consent until the end of the study (i.e., the safety telephone call). Serious AEs occurring after the end of the study and coming to the attention of the PI must be reported only if they are considered (in the opinion of the PI) causally-related to the investigational drug.

6.1.2.8 Follow-up of Adverse Events

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a

level acceptable to the Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up or until the patient has died.

6.1.2.9 Pregnancy

Women are advised not to become pregnant during the trial and for at least 3 days after the end of the trial period. A pregnancy which occurs during the trial is a reason for study withdrawal. Although a pregnancy is not considered as an adverse event, it is the responsibility of investigators or their designees to report any pregnancy that occurs during the trial or within 3 days of completing the trial. All subjects 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 adverse events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported. The investigator should fax or email the Pregnancy Form to [redacted] Safety within 24 hours of being notified.

6.1.3 Clinical Laboratory Assessments

6.1.3.1 Sample Collection

Blood samples will be collected for clinical laboratory testing at the time points indicated in the Schedule of Assessments (Table 4). Safety laboratory variables are listed in Table 3.

Table 3 Safety Laboratory Assessments

Hematology	erythrocytes MCV MCH neutrophils eosinophils basophils	lymphocytes monocytes platelets leukocytes hemoglobin hematocrit PT INR
Clinical chemistry	Albumin BUN creatinine CPK hs-CRP triglycerides urea uric acid cholesterol	**Electrolytes:** sodium potassium **Liver Enzymes:** ALT AST ALP bilirubin GGT serum proteins
Urinalysis	appearance color	leukocytes blood

	bilirubin pH protein glucose ketones	nitrite specific gravity urobilinogen
Serology	HIV type 1 and type 2 HAV IgM HBsAg HCV	
Pregnancy test	For women of childbearing potential only at the first Screening Visit	
Drugs of Abuse Screen (urine)	amphetamines benzodiazepines marijuana cocaine opioids	

AST = aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; BUN = blood urea nitrogen; CPK = creatinine phosphokinase; GGT = γ-glutamyl transferase; HAV IgM= anti hepatitis A virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitive c-reactive protein; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; PT = prothrombin time

6.1.3.2 Sample Storage and Shipping

Except where noted, all samples for laboratory assessments will be shipped to and processed by a central laboratory. All details regarding laboratory sample preparation and shipment will be provided by the central laboratory and all other blood and urine samples will be collected according to the laboratory manual provided by the central laboratory and according to the Schedule of Assessments (Table 4).

The laboratory evaluations that are to be performed locally at the study site (e.g., urinalysis and pregnancy testing by means of serum human chorionic gonadotropin [hCG] and urine hCG) should be performed according to the site's local laboratory protocol.

6.1.3.3 Results of Laboratory Assessments

The central laboratory will provide the results of the testing to the study site to allow for the PI to confirm patient eligibility, manage enrolled patients and assess the clinical significance of each laboratory value/result. In the event of abnormal clinical laboratory values, the PI will make a judgment as to whether or not the abnormality is clinically significant.

Approximately 1 week after Visit 2, the results of the laboratory tests will be returned to the site for verification of patient eligibility.

6.1.3.4 Urine Tests

Urine tests will be processed either centrally or locally, as noted below:

- Urine hCG (women of childbearing potential only at Visits 3, 4, 5, 6 and 7) will be processed by a local laboratory
- Urinalysis will be processed by a local laboratory
- Urine drugs of abuse screening will be processed at a central laboratory.

6.1.4 Vital Signs

The following vital signs will be assessed at time points described in the Schedule of Assessments (Table 4):

- Sitting blood pressure (systolic and diastolic; mmHg) (measured in triplicate at Visit 1 and a single measurement at all other visits)
- Pulse (beats per minute) (measured in triplicate at Visit 1 and a single measurement at all other visits)
- 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. A 5-minute rest period in between vital signs and ECG measurements is recommended.

6.1.5 Twelve-lead Electrocardiograms

Electrocardiograms will be performed locally at the study site in accordance with the Schedule of Assessments (Table 4). The 12-lead ECG equipment will be set to 25 mm/sec and 10 mm/mV and ECGs will be recorded with patients in the recumbent position and resting. Patients should be in this resting position for 5 minutes before ECG recording and performed before any blood draw that occurs at the same visit.

Measures will be taken to eliminate baseline tremor, as it may interfere significantly with the quality of the interpretation. Before electrode placement, the 10 anatomical sites will be prepared to allow for proper skin/electrode interface. Patients with excessive hair will be dry shaven, as needed.

Electrocardiogram recordings will be taken in triplicate at the Screening Visit and as a single recording at all other visits.

6.1.6 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Assessments (Table 4). Patients' body weight will be recorded during all physical examinations. Height will be recorded at Screening Visit only).

6.2 Efficacy Variables

6.2.1 Blood Samples

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.

For the primary efficacy variable, blood samples for measurement of ALT will be collected at the time-points specified in the Schedule of Assessments (Table 4). Refer to Section 6.1.3 for information about sample collection, shipping and storage and results of sample collection for ALT.

Samples for secondary and exploratory efficacy variables will be collected as follows:

Insulin resistance and glycemic control: includes fasting (at least 8 hours) insulin, fasting plasma glucose, HbA1c, C-peptide, HOMA-IR and HOMA-ß. The results of the fasting plasma glucose, HbA1c, HOMA-IR and HOMA-ß will be blinded to site. Results of Insulin and C-Peptide will not be blinded.

Lipoprofile: includes fasting (at least 8 hours) LDL, VLDL, HDL, total cholesterol, non-HDL cholesterol, apo A and apo B. The results of the lipoprofile (except total cholesterol) will be blinded to site. Serum triglyceride results will not be blinded.

CK-18 and APRI: includes CK-18, AST and platelet count

ELF score: serum samples. Enhanced liver fibroses score is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease.

Full details regarding laboratory sample preparation and shipment will be provided by the central laboratory.

6.2.2 Quality of Life

Subjective QoL assessments will be measured using the SF-36 version 2.0 (See Appendix 1: Quality of Life Assessment Questionnaire), 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.

6.2.3 Transient Elastography/FibroScan

Liver stiffness measurements will be performed by transient elastography using the FibroScan (Echosens, Paris, France). The appropriate FibroScan measurement probe should be used (i.e., M or XL) based on the manufacturer's recommendation for probe choice according to chest circumference and age. FibroScan is optional and performed only sites with machines available at sites.

Patients will fast for 3 hours before the transient elastography/FibroScan procedure. For the liver stiffness measurements, patients will be in dorsal decubitus position with the right arm in maximal abduction. The exam begins with placement of the probe along the intercostal space to obtain a view of the right lobe of the liver. Once an area of at least 6 cm thick and free of large vascular structures or gallbladder is identified, 10 measurements should be obtained. A FibroScan exam will only be considered acceptable if it results in 10 measurements with a 70% success rate, and the interquartile range is less than 30% of the value of the median or controlled attenuation parameter (CAP) will be simultaneously measured with liver stiffness using the same probe.

6.2.4 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). On the other hand, H1-MRS only measures liver fat content in a small region of interest. Another benefit of PDFF over H1-MRS is that the former may be performed in a few seconds as a breath-hold scan. H1-MRS, together with the shimming time required prior to the scan, takes at least 30 minutes to complete.

6.3 Pharmacokinetics Assessment

Pharmacokinetics of Saroglitazar Magnesium following first dose and last dose in patients with NAFLD/NASH will be performed. 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 4, 5 and 6. The pharmacokinetics sampling will only be collected in the approximately 32 subjects participating in the PK evaluation.

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

i. Peak Plasma concentration (Cmax)
ii. Time to reach peak Plasma concentration (Tmax)
iii. Area under Plasma concentration vs. time curve till the last time-point (AUC0-t)
iv. Area under Plasma concentration vs. time curve extrapolated to the infinity (AUC0-∞) after first dose
v. Area under plasma concentration vs. time curve in a 24 h dosing interval (AUCtau)
vi. Elimination rate constant (λz)
vii. Elimination half-life (t1/2)
viii. Apparent Volume of distribution (Vd/F)
ix. Apparent Clearance (CL/F)
x. Minimal or Trough plasma concentration (Cmin) -for last dose only
xi. Accumulation index calculated as a ratio of AUCtau(last dose)/AUCtau(first dose)
xii. Fluctuation index.

6.4 Biobanking Samples for Exploratory Analyses

At each visit, approximately 3.5 mL of whole blood (1 mL of serum) will be collected for biobanking. It means a total of 24.5 mL of whole blood will be collected at Visits 1 through 7 for biobanking and exploratory analyses.

6.5 Total Amount of Blood

The total amount of blood drawn for each patient over the study will be less than 500 mL.

7. STUDY CONDUCT

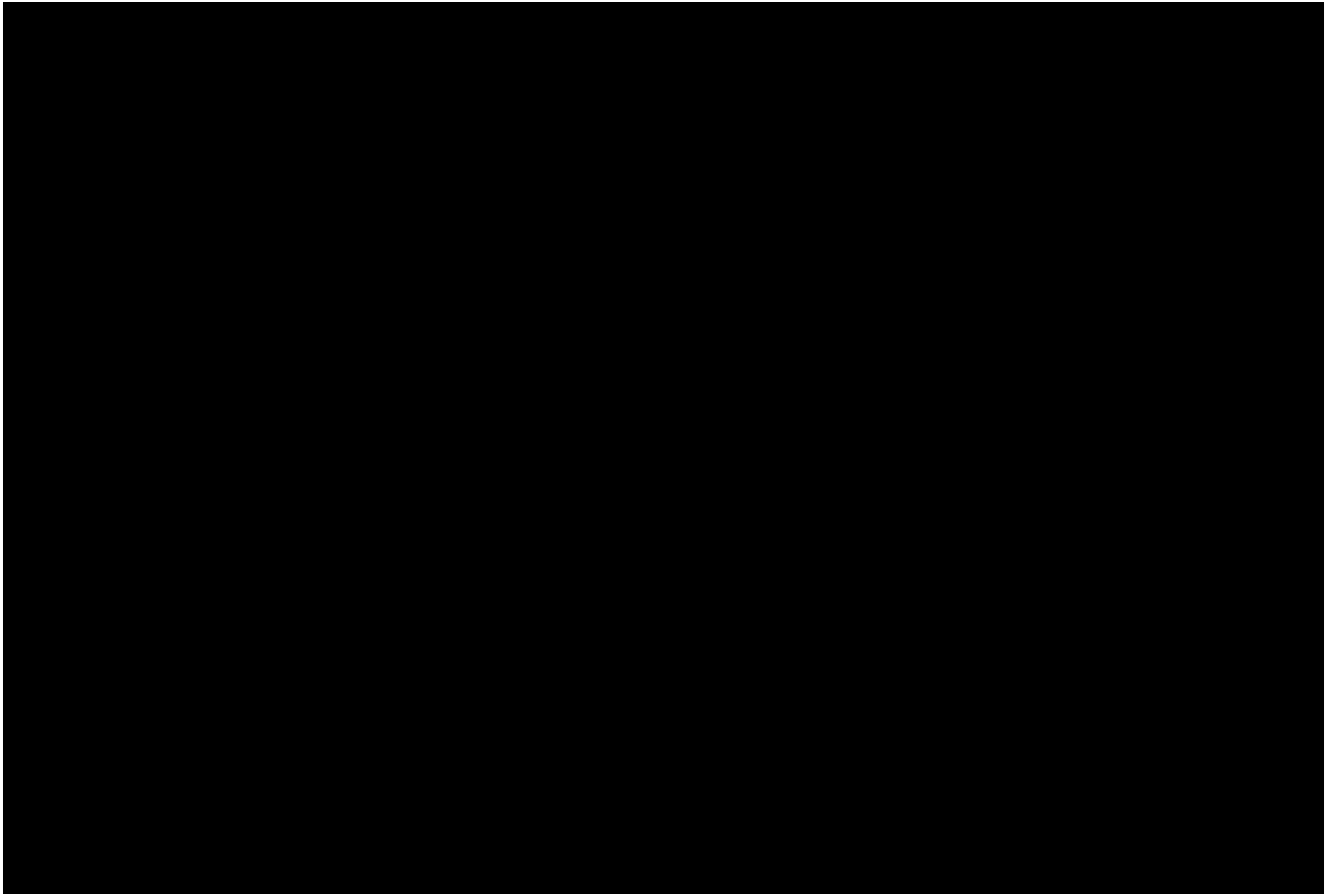
7.1 Schedule of Assessments

The study consists of an optional Pre-screening, a 35-day Screening Period, a Treatment Period (Day 1 through Day 112) and a telephone follow-up. Therefore, the maximal study duration for an individual patient will be up to 154 days or 22 weeks.

Please Table 4 for the Schedule of Assessments.

Table 4 Schedule of Assessments

[redacted]



[redacted]

7.2 Data Monitoring Committee

Safety data will be reviewed regularly by a Data Monitoring Committee (DMC). The Data Monitoring Committee comprised of an unblinded independent statistician and hepatologist who will review period reports from the EDC. The formal structure and conduct of DMC will be according to a previously agreed upon remit.

7.3 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 Investigators. The blinded medical review of known or suspected MACE will primarily focus on CV death, myocardial infarction, cerebrovascular accident (stroke), and hospitalization for heart failure.
A detailed CAC Charter and adjudication process will be described in a separate document.

8. STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses summarized below. Any deviations from the planned analyses will be described and justified in the final clinical study report.

8.1 Study Population

8.1.1 Disposition of Patients

The number of patients who will be enrolled into the study, patients included in each analysis set, and subjects who completed/prematurely discontinued the study, as well as the reason for discontinuation, will be presented by treatment and overall using frequency counts and percentages. Percentages will be based on the number of patients randomized. In addition listings will be provided for study discontinuation, subject disposition and subject populations.

8.1.2 Patient Characteristics

Patient characteristics will include a summary and listing of the following:

- Demographics (including gender, age, race, ethnicity)
- Baseline characteristics (including height, weight, BMI)
- Medical history
- Prior and concomitant medications.

8.1.3 Protocol Deviations

Protocol deviations will be listed by patient.

8.1.4 Analysis Populations

Randomized Set: The Randomized Set will consist of all subjects randomized into the study.

Safety Analysis Set: The Safety Analysis Set will consist of all patients who are known to have received at least 1 dose of study treatment, with patients grouped according to the actual treatment received.

Full Analysis Set (FAS): The FAS will consist of all patients who have been randomized, taken at least 1 dose of the study treatment and have provided efficacy data for at least 1 endpoint.

Patients who receive study drug different from that to which they are randomized will be included in the group to which they are randomized.

Per Protocol (PP) analysis set: The PP Analysis Set will consist of all patients in the FAS who have additionally completed the double-blind treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome. The PP Analysis Set will be defined before unblinding the study.

Enrolled Set: The Enrolled Set will consist of all patients who are enrolled.

8.2 General Considerations

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA).

Data may be summarized by treatment group, and in addition, may be summarized by time (nominal).

It is planned that at least 104 subjects will be enrolled at multiple clinical centers in USA. The data from different centers will be pooled. The data summaries and statistical analyses will not be performed by center.

Continuous data will be summarized by treatment group using descriptive statistics (number of patients, mean, median, standard deviation, minimum and maximum). Categorical data will be summarized by patient counts and percentages.

If not otherwise stated, Baseline will be the last available pre-dose value or, if missing, the Screening value. Measurement specific baseline values will be defined in the SAP.

8.3 Safety Analyses

All safety parameters will be listed by treatment group and patient.

All study drug administration information will be listed.

Review of alcohol consumption will be listed.

8.3.1 Adverse Events

Adverse events will be listed. The number and percent of patients experiencing an event will be tabulated for each system-organ class and preferred term. Adverse events will also be tabulated according to intensity and causality. The Adverse Events leading to discontinuation and SAEs will also be summarized by treatment group.

Adverse Events leading to discontinuation and SAEs will be listed separately.

8.3.2 Clinical Laboratory Tests

Individual data listings of laboratory results will be presented for each patient. Clinically significant laboratory test abnormalities that were considered AEs by the Investigator will be presented in the AE listings.

Observed results and changes from baseline in laboratory data will be tabulated by treatment group. Laboratory values will be categorized as normal, high or low in relation to the normal range values. Change from the Baseline value and each post-treatment assessment will be presented in shift tables for categorized laboratory results (normal, low and high). Values outside the reference range will be flagged in the listings. The normal range values will be reported.

Additional laboratory tests (including pregnancy tests) will be listed.

8.3.3 Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented for each patient. Individual clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE listings.

Observed values as well as change from baseline data will be summarized descriptively by vital sign variables will be presented by treatment group in tabular format.

8.3.4 Electrocardiogram

Twelve-lead ECG data (observed and change from baseline) will be listed for each patient and time-point. Observed values will be summarized descriptively in tabular format by treatment group.

8.3.5 Physical Examination

Abnormal physical exam findings will be listed.

8.4 Efficacy Analyses

All efficacy analyses will be based primarily on the FAS, and analyses based on the PP Analysis Set will be secondary to this, as required.

8.4.1 Primary Efficacy Analyses

The primary analysis for the primary efficacy endpoint will be based on the FAS. The primary efficacy endpoint in this study is percent change from baseline to Week 16 in serum ALT levels and will be analyzed using an analysis of covariance (ANCOVA) model with treatment as factor and baseline ALT levels as covariate. The comparison of interest is Saroglitazar Magnesium 1 mg, 2 mg and 4 mg versus placebo at Week 16.

The statistical null-hypothesis regarding the primary endpoint is as follows:

H_0: $-\mu_{\text{Saroglitazar Magnesium}} \leq -\mu_{\text{placebo}}$

and

H_1: $-\mu_{\text{Saroglitazar Magnesium}} > -\mu_{\text{placebo}}$

where $\mu_{\text{treatment}}$ group is the mean percent change from baseline to Week 16 in serum ALT levels with Saroglitazar Magnesium (1 mg, 2 mg and 4 mg) and placebo. Note: Improvement in percent change from baseline to Week 16 in ALT levels is indicated by $\mu_{\text{treatment}}$ group < 0. Hypotheses will be tested at a 1-sided nominal significance level-alpha of 0.05.

Least squares (LS) means for each treatment group and associated standard errors will be derived. Differences in LS means will be calculated and associated 2-sided 90% confidence intervals will be provided. These will be derived from the calculation of Type III LS Means from ANCOVA and presented. One-tailed P value will also be presented to test the alternative hypothesis that Saroglitazar Magnesium is superior to placebo.

Missing values will be imputed by carrying forward the last observation value after baseline.

Secondary analyses (of the primary endpoint) will be analyzed using a similar analysis in the PP Analysis Set.

Residual analysis will be used to check assumptions for the ANCOVA model. Should any of the assumptions of the analysis method not be adequately met, an alternative procedure will be used and fully documented.

8.4.2 Secondary Efficacy Analyses

Due to this being a proof-of-concept (PoC) study, no adjustment of any P values will be made to account for inflation of the Type 1 error rate arising from testing multiple endpoints, or testing

the same endpoint at different times. For each endpoint, the comparison will be conducted using a significance level (alpha) set at 0.1 (2-sided) or equivalently 0.05 (1-sided).

Each secondary efficacy endpoint will be summarized by treatment group at each time-point, as appropriate.

The following endpoints will be analyzed similar to primary analysis:

- Change in liver fat at Week 16 as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF)
- Percentage change from baseline and absolute change from baseline in serum ALT levels at Week 4, week 8 and Week 12 of treatment
- Percentage change from baseline and absolute change from baseline in CK-18 fragment, ELF score and APRI at Week 8, and Week 16 after treatment
- Absolute change from baseline in AST/ALT ratio at Week 4,Week 8, Week 12 and Week 16 after treatment
- Pharmacokinetics of Saroglitazar following first dose and last dose in approximately 32 patients (approximately 8 from each dose arm) with NAFLD/NASH
- Absolute Change from baseline in the SF-36 8 domain scores and 2 component scores (separate analyses) at Week 16 after treatment.

Above analyses will also be supported by simple summaries (n, mean, standard deviation, median, minimum and maximum) at each visit, without covariate adjustment.

Proportions of patients with percentage reductions of ≥25% and ≥50% from baseline in ALT levels at Week 4, Week 8, Week 12 and Week 16 will be analyzed using logistic regression including terms for baseline ALT levels and treatment. Endpoints based on proportion of patients will be summarized. For the categorical data, descriptive summary statistics will be, summarizing the number and percentage of patients in each category at each visit.

Descriptive statistics will be provided for each Pharmacokinetic parameter (as detailed in Section 6.3).

8.4.3 Exploratory Efficacy Analyses

The individual values of the exploratory endpoints will be listed and summary statistics will be calculated for each treatment group. The exploratory analyses will be based primarily on the FAS, and analyses based on the PP Analysis Set will be secondary to this, as required.

8.5 Interim Analyses

No interim analysis is planned.

8.6 Determination of Sample Size

The endpoint that determines the sample size for this trial is the percentage change from baseline to Week 16 in serum ALT levels.

Descriptive statistics was calculated for the percentage change from baseline to Week 12 in serum ALT levels from a clinical study on Saroglitazar Magnesium in NASH patients (Protocol No.: ZYH1.09.004.01. PROT). The mean percentage change from baseline to Week 12 in ALT (U/L) with Saroglitazar Magnesium 4 mg was -49.36 and standard deviation was 24.03.

Sample size is based on a 1-sided t-test (2 independent samples) at the 5% significance level for the percentage change from baseline between Saroglitazar Magnesium (1 mg, 2 mg 4 mg) and placebo at Week 16 (a 1 sided test ignores the small probability of a significant result in the "wrong" direction [i.e., superiority of placebo over Saroglitazar Magnesium]. Because this is a PoC study, this approach is acceptable).

A sample size of 23 patients in each arm will provide 95% power to detect a difference in mean of 25% of ALT (U/L) levels between Saroglitazar Magnesium 4 mg and placebo assuming a common standard deviation of 25% approximately. Therefore, allowing for 10% attrition between randomization and inclusion in the full analysis set, 104 patients will be required in the study (26 randomly assigned to placebo and 26 randomly assigned to each Saroglitazar group i.e. 1 mg, 2 mg and 4 mg).

9. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRF for this study must be consistent with the patients' source documentation (i.e., medical records).

9.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using CRFs. Data from external sources (such as laboratory data) will be imported into the database. Once the CRF clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manger will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the CRF page.

The specific procedures to be used for data entry and query resolution using the CRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the CRF.

9.2 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the CRFs promptly. All source documents from which CRF entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments and ECG recordings.

Data that will be entered directly into the CRF (i.e., for which there is no prior written or electronic record of data, such as QoL assessments) are considered to be source data.

The original CRF entries for each patient may be checked against source documents at the study site by the [redacted] site monitor.

The specific procedures to be used for data entry and query resolution using the CRF will be provided to study sites in a training manual. In addition, site personnel will receive training on the CRF.

9.2.1 Data Collection

The Investigators (and appropriately authorized staff) will be given access to an online web-based EDC) system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to each individual's role throughout the study. In general, only the investigator and authorized staff will be able to enter data and make corrections in the CRFs.

The CRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the CRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The investigator must verify that all data entries in the CRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable or unknown, the Investigator should indicate this in the CRF.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the investigator will be required to electronically sign off the clinical data.

Data about all study drug dispensed to the patient and any dosage changes will be tracked on the CRF.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare CRF entries and individual patient's medical records, assess drug accountability and ensure that the study is being conducted according to pertinent regulatory requirements. Case report form entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the CRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures [redacted] and the Sponsor of the necessary support at all times.

9.4 Data Processing

All data will be entered by site personnel into the CRF (as detailed in Section 9.2.1).

The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated on the basis of signed corrections.

Previous and concomitant medications will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Previous and concomitant diseases as well as AEs will be coded using MedDRA.

The version of the coding dictionaries will be provided in the Clinical Study Report.

9.5 Archiving Study Documents

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since

the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the Good Clinical Practice guidelines. The study also will be carried out in keeping with local legal requirements.

9.7 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the CRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

9.8 Protocol Approval and Amendment(s)

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB approval before implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug under which the study is being conducted.

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

9.9 Confidentiality Data Protection

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on CRF and other documents submitted to [redacted] by their patient number, initials and/or birth date, not by name. Documents not to be submitted to [redacted] that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.10 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to all parties – Regulatory Authorities, Investigators and the IRB.

A significant safety issue is one that has a significant impact on the course of the clinical study or program (including the potential for suspension of the development program or amendments to protocols) or warrants immediate update of informed consent.

9.11 Publication Policy

By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

10. REFERENCE LIST

Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, Haflidadottir S, Day CP, George J. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013; 145(4):782-9.

Bellentani S, Dalle Grave R, Suppini A, Marchesini G, Fatty Liver Italian Network. Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. Hepatology 2008; 47(2):746-54.

Brunt EM, Tiniakos DG. Pathological features of NASH. Frontiers in bioscience: a journal and virtual library. 2005;10:1475-84.

Bydder M, Yokoo T, Hamilton G, et al. Relaxation effects in the quantification of fat using gradient echo imaging. Magn Reson Imaging. 2008;26(3):347-59.

Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012; 55(6):2005-23.

Hu FB. Globalization of Diabetes: The role of diet, lifestyle, and genes. Diabetes Care. Published online. 2011;34(6):1249–1257.

Idilman IS, Aniktar H, Idilman R, et al. Hepatic steatosis: quantification by proton density fat fraction with MR imaging versus liver biopsy. Radiology. 2013;267(3):767-75.

Kang GH, Cruite I, Shiehmorteza M, et al. Reproducibility of MRI-determined proton density fat fraction across two different MR scanner platforms. J Magn Reson Imaging. 2011;34(4):928-34.

Liu CY, McKenzie CA, Yu H, Brittain JH, Reeder SB. Fat quantification with IDEAL gradient echo imaging: correction of bias from T(1) and noise. Magn Reson Med. 2007;58(2):354-64.

Mashhood A, Railkar R, Yokoo T, et al. Reproducibility of hepatic fat fraction measurement by magnetic resonance imaging. J Magn Reson Imaging. 2013;37(6):1359-70.

Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999; 116(6):1413-9.

McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clin Liver Dis 2004; 8(3):521-33.

Musso G1, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011; 43(8):617-49.

Noureddin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology. 2013;58(6):1930-40.

Sanyal AJ, Brunt EM, Kleiner DE, Kowdley K, Chalasani N, Lavine J, Ratziu V, McCullough A. Endpoints and clinical trial design for nonalcoholic steatohepatitis. Hepatology 2011; 54(1): 344–353.

Tang A, Tan J, Sun M, et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. Radiology. 2013;267(2):422-31.

Yokoo T, Bydder M, Hamilton G, et al. Nonalcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5 T. Radiology. 2009;251(1):67-76.

Yokoo T, Shiehmorteza M, Hamilton G, et al. Estimation of hepatic proton-density fat fraction by using MR imaging at 3.0 T. Radiology. 2011;258(3):749-59.

Yu H, McKenzie CA, Shimakawa A, et al. Multiecho reconstruction for simultaneous water-fat decomposition and T2* estimation. J Magn Reson Imaging. 2007;26(4):1153-61.

Wieckowska A1, Feldstein AE. Nonalcoholic fatty liver disease in the pediatric population: a review. Curr Opin Pediatr 2005; 17(5):636-41.

11. APPENDICES

11.1 Appendix 1: Quality of Life Assessment Questionnaire

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

11.2 Appendix 2: 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