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Clinical Trial Protocol

Zydus Discovery DMCC

[redacted] Trial No.:	SARO.17.004
Protocol No.:	SARO.17.004.02.PROTOCOL
Superseded Protocol No and Date	SARO.17.004.01.PROTOCOL Version 1.0; dated 12 December 2017
Reference IND No.	128791
Supersedes Protocol No.:	Not applicable
Investigational: product(s)	Saroglitazar Magnesium
Scientific Title:	A Phase 2, Prospective, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Saroglitazar Magnesium 2 mg and 4 mg in Patients with Non-alcoholic Steatohepatitis.
Public Title:	Saroglitazar Magnesium 2 mg and 4 mg in the treatment of Non-Alcoholic Steatohepatitis
Clinical Phase:	2
Sponsor	Zydus Discovery DMCC Unit No 909, Armada 2 Plot No: JLT-PH2-P2A, Jumeirah Lakes Towers Dubai UAE P.O Box 113536
Sponsor's Representative	Deven V Parmar, MD FCP [redacted]

Principal Investigators	[redacted]
Sponsor's Medical Expert:	[redacted]
Clinical Laboratory	[redacted]
Data Management and Statistical Analysis:	[redacted]
Date of Protocol:	02 August 2018
Planned Date of Trial:	January 2019
Confidential	*This protocol is the property of Zydus Discovery DMCC and may not - in full or in part - be retrieved, passed on, reproduced, published or otherwise used without the express permission of Zydus Discovery DMCC.*

CLINICAL TRIAL PROTOCOL SUMMARY

Name of Sponsor:	Zydus Discovery DMCC Unit No 909, Armada 2 Plot No: JLT-PH2-P2A, Jumeirah Lakes Towers Dubai UAE P.O Box 113536
Name of Investigational product:	Saroglitazar Magnesium 2 mg and 4 mg
Name of active ingredient of investigational product	Saroglitazar Magnesium
Name of the comparator drug	Placebo
Name of active ingredient of comparator product	Placebo
Potential Indication	Treatment of Non-alcoholic Steatohepatitis
Study Subjects	Patients with Non-alcoholic Steatohepatitis
Number of subjects	15
Number of site(s)	Multicenter
Study Number:	SARO.17.004
Planned treatment Period	24 Weeks
Study Duration	32Weeks
Title of study: A Phase 2, Prospective, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Saroglitazar Magnesium 2 mg and 4 mg in Patients with Non-alcoholic Steatohepatitis.	
Clinical phase: Phase 2	

Primary Objective:

To evaluate the changes in NAFLD Activity Score (NAS) at week 24 from baseline and with no worsening of fibrosis in NASH patients.

Secondary Objectives:

- To evaluate the percentage of responders in the treatment groups.
- To evaluate the percentage of responders, defined as the disappearance of steatohepatitis over the time period up to Week 24.
- Changes from baseline to Week 24 in Saroglitazar Magnesium 2 mg and 4 mg for the following parameters:
    - Stage of steatosis, lobular inflammation and ballooning.
    - Stages of fibrosis.
    - Liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, Gamma-glutamyl transferase, direct bilirubin, total proteins and albumin).
    - Lipid profile parameters (triglyceride, small dense low density lipoprotein, high density lipoprotein, low density lipoprotein, very low density lipoprotein, total cholesterol and non HDL cholesterol Apo lipoprotein A1 and Apo lipoprotein B).
    - Insulin resistance and glycemic control parameters (fasting plasma glucose, glycosylated hemoglobin, fasting insulin, C-peptide, adiponectin, homeostasis model assessment beta and homeostasis model assessment for insulin resistance).

- To assess the safety of Saroglitazar Magnesium in patients with non-alcoholic steatohepatitis over 24 weeks of treatment.

Criteria for Safety:

- Frequency and severity of adverse events
- Physical examination and body weight
- Vital signs
- Clinical laboratory testing (hematology, clinical chemistry, serology and urinalysis).
- 12-lead electrocardiogram (ECG).

Criteria for inclusion/exclusion:

INCLUSION CRITERIA

1. Patients able to provide written informed consent for participation in this trial.
2. Males or females, 18 to 75 years of age, both inclusive.
3. Female must be either of non-child bearing potential (surgically sterilized at least 6 months prior to screening or postmenopausal) or using one or more methods of contraception.
4. Histologic confirmation of NASH without cirrhosis (fibrosis stage 0, 1, 2, or 3) from liver biopsy performed either during the screening period or no more than 6 months prior to the first visit, with a NAS of ≥4 and a score of at least 1 in each (steatosis scored 0-3, ballooning scored 0-2, and lobular inflammation scored 0-3). If biopsy was performed within 6 months of screening, the slides, biopsy material or block should be available for baseline documentation. Such patients, whose historical biopsy report is available, should not use medications suspected of having an effect on NASH for at least 3 months prior to the screening.
5. BMI ≥25 kg/m^2.
6. For hypertensive patients, blood pressure must be controlled by a stable dose of antihypertensive medications for at least 3 months prior to screening (and the stable dose can be maintained throughout the study)
7. Patients with type 2 diabetes mellitus may be included if they fulfil the following criteria;
    a. Stable therapeutic regimen as defined by no changes in oral agents or dose for at least 3 months before screening and the stable dose can be maintained throughout the study.
    b. HbA1c ≤ 9.5%
8. Patients agree to comply with the study procedure.

EXCLUSION CRITERIA

1. Pregnant and lactating female.
2. Positive pregnancy test.
3. Patients with history of myopathies or evidence of active muscle diseases.
4. Patients with history of alcohol consumption of >30 gm/day for men, >20 gm/day for women for consecutive previous 2 years and/or drug abuse.
5. Known allergy, sensitivity or intolerance to the study drug or formulation ingredients.
6. Participation in an interventional clinical study and/or receipt of any investigational medication within 3 months prior to screening.
7. History of malignancy in the past 5 years and/or active neoplasm with the exception of superficial, non-melanoma, skin cancer.

8. Any of the following laboratory values at screening:
    a. Direct bilirubin >1.5 mg/dL,
    b. Serum albumin <2.5 g/dL.
    c. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2.
    d. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >200 IU/L.
    e. Patient with international normalized ratio (INR) >1.5.
    f. Creatinine kinase ≥ 1.5 ULN.
    g. Lipase ≥ULN.
    h. Amylase ≥ ULN.
9. Unstable cardiovascular disease, including:
    a. unstable angina, (i.e., new or worsening symptoms of coronary heart disease within the 3 months preceding screening), acute coronary syndrome within the 6 months preceding Screening, acute myocardial infarction within the 3 months preceding screening 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 screening
    b. history of (within 3 months preceding Screening) or current unstable cardiac dysrhythmias
    c. uncontrolled hypertension (systolic blood pressure [BP] > 155 mmHg and/or diastolic BP > 95 mmHg)
    d. Stroke or transient ischemic attack within the 6 months preceding screening.
10. Previous history of bladder disease and/or hematuria.
11. Previous liver biopsy that demonstrated presence of cirrhosis or radiologic imaging consistent with cirrhosis or portal hypertension.
12. Type 1 diabetes mellitus.
13. Use of drugs that are known CYP2C8 inhibitors/substrate.
14. Use of drugs associated with a clinical or histological picture consistent with fatty liver disease or NASH for more than 12 consecutive weeks in the 1 year prior to start of the study; (these include amiodarone, tamoxifen, methotrexate, glucocorticoids, anabolic steroids, tetracyclines, estrogens, valproate/valproic acid, chloroquine, anti-HIV drugs).
15. History of thyroid disease (hypothyroid patients who are euthyroid on thyroid hormone replacement can be included).
16. History of, or current, cardiac dysrhythmias.
17. History of bariatric surgery, or undergoing evaluation for bariatric surgery.
18. Patients with a >10% weight loss in the 3 months prior to screening.
19. 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, coronary artery disease, HIV or active gastrointestinal conditions that might interfere with drug absorption).
20. Patients on any treatment with other drugs used for treatment of NASH [pentoxyphyllin, ursodeoxycholic acid, antioxidants such as vitamin E (>800 IU/day), glutathione, orlistat, betaine, incretin mimetics or non-prescribed complementary alternative medications (including dietary supplements, megadose vitamins, herbal preparations and special teas)] or any medicine in clinical trials for NASH. *(However, patients who are taking stable dose of vitamin E for at least 3 months prior to screening will be enrolled in the study).*
21. History of other causes of chronic liver disease [autoimmune, primary biliary cirrhosis, hepatitis B virus (HBV) and hepatitis C virus (HCV), Wilson disease, alpha-1-antitrypsin deficiency, hemochromatosis etc.

Methodology:

This is a randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of Saroglitazar Magnesium 2 mg and 4 mg in patients with NASH. This study will be initiated after obtaining the approvals of Institutional Ethics Committee/Institutional Review Board (IEC/IRB) and the local regulatory authority.

It is the responsibility of the Principal Investigator (PI) to ensure that the study is conducted in accordance with the protocol, International Council for Harmonisation Good Clinical Practice and all applicable regulatory requirements. Informed consent will be obtained before the start of any study related procedures.

As per the contemporary guidelines, the Investigator shall maintain Source Documents (SD), Site Master File (SMF), Informed Consent Forms/Documents (ICF/ICD) and other logs/forms during the conduct of a study.

All laboratory reports should be reviewed by the PI and/or his/her designee and any abnormal findings should be addressed. All protocol deviations occurring on the study shall be documented and the Sponsor and IEC/IRB informed.

Patients clinically suspected of NASH will be invited for a screening programme for inclusion in the study. Patients will be screened according to the inclusion and exclusion criteria. Clinical evaluation will be conducted for baseline characteristics and anthropometry measurements such as body weight and height.

After clinical evaluations, all baseline safety and efficacy parameters will be recorded as per Visit Schedule. All laboratory collections will be performed following overnight fasting (at least 8 hrs).

Following confirmation of all clinical and laboratory inclusion and exclusion criteria, patients will continue into the screening period. During the screening period liver biopsy will be performed. However, if a biopsy was performed within 6 months the slides and biopsy material, or block, must be made available for baseline documentation. Such Patients, whose historical biopsy report is available, should not use medication suspected of having an effect on NASH from the 3 months prior to the screening.

Liver biopsy will be performed to confirm the diagnosis of NASH and record a baseline NAFLD Activity Score (Appendix 2). The histological evidence of NASH is defined as NAS $\geq$ 4 with a minimum score of 1 for all of its three components [steatosis, hepatocyte ballooning and lobular inflammation].

Following confirmation of inclusion/exclusion criteria and upon histological confirmation of NASH by liver biopsy, patients will be enrolled into the study.

Eligible patients will be randomly assigned to receive Saroglitazar Magnesium 2 mg or 4 mg or placebo in a 2:2:1 ratio for 24 weeks.

Upon completion of 24 weeks of treatment, liver biopsy will be performed and the NAFLD Activity Score recorded (Appendix 2).

The scheduled visits during this study will be as follows:

- Visit 1: Screening Visit [-4 Week (-28 Days)],
- Visit 2: Enrollment Visit (Day 1± 7 Days /Week 0),
- Visit 3: Day 43/Week 6 ± 7 Days,
- Visit 4: Day 85/Week 12 ± 7 Days,
- Visit 5: Day 127/Week 18 ± 7 Days,
- Visit 6: Day 169/Week 24 ± 7 Days,
- Visit 7: Follow-up Visit: Day 197/Week 28 ± 7 Days,

If the patient has consumed restricted medications but is otherwise considered eligible to be enrolled in this study by the PI, a minimum of 1 month wash out period will be instituted before the screening visit. All unscheduled visits will be reported in the Case report form.

Patients will be advised to follow a stable lifestyle. No change in the intensity of lifestyle (Diet/Exercise) will be allowed during the period of study. Patient will be monitored for safety and efficacy parameters as per Visit Schedule.

If further investigations are required in case of any AE, Investigator is advised to assess the AE and take necessary action. Patients are advised to contact the Investigator for any complaints.

Visit Schedule

- **Screening Visit 1 [-4 Week (-28 Days)],**

a. All patients will be required to sign and date the IRB/IEC approved ICF after all study-related procedures have been explained by the PI/designee and understanding the contents.
b. The informed consent process will be documented in the Source Documents, ICF and other relevant logs and signed and dated by the PI/ or delegated study team members on site. Prior to subject participation in the study, written informed consent will be obtained from each subject according to the regulatory and legal requirements of the participating country, including state-specific requirements.
c. Patients will be screened for eligibility; those qualifying will be invited to participate in the study.
d. Demographics, vitals, physical examination, medical history, prior and concomitant medication review will be recorded.
e. Clinical evaluation will be done for baseline characteristics and body weight will be recorded.
f. After clinical evaluations, all baseline safety and efficacy parameters will be assessed as per Visit Schedule. All laboratory investigations will be performed on overnight fasting blood samples. Electrocardiograph (ECG) will be performed.
g. Serum pregnancy test will be done for females of child-bearing potential.
h. Patients are advised to maintain a stable life-style.
i. Adverse events will be recorded.

Liver biopsy Visit

a. Liver biopsy will be done after the patient passes all other inclusion and exclusion criteria to

confirm NASH diagnosis and record a baseline NAFLD Activity Score (Appendix 2). If biopsy is done within 6 months, the slides, biopsy material or block should be available for baseline documentation. Such patients, whose historical biopsy report is available, should not use medication suspected of having an effect on NASH from the 3 months prior to the Screening.

b. Liver biopsy will be performed with a 16 gauge (1.6 mm) needle with Ultrasound guidance. The length of the specimen collected should be approximately 1.5 cm. The specimen will be read centrally for NAFLD Activity Score by pathologist at Virginia Commonwealth University, Medical Center, 1250 E Marshall St Richmond, VA 23298 United States.

- **Visit 2 Enrollment Visit [Week 0, Day 1+/- 7 Days]**

a. Patients satisfying the inclusion and exclusion criteria will be randomly assigned to receive Saroglitazar Magnesium 2 mg or 4 mg or placebo.
b. Patients will undergo physical examination.
c. Concomitant medications will be assessed.
d. Vitals signs will be recorded.
e. Body weight will be recorded.
f. ECG will be performed.
g. Adverse events will be recorded.
h. Urine pregnancy test will be performed for females of child-bearing potential.
i. Safety and efficacy parameters will be assessed as per Visit Schedule.
j. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).
k. Patients are advised to maintain a stable life-style.

- **Visit 3 [Day 43 (+/- 7 Days)]**

a. Patients will undergo physical examination.
b. Vitals signs will be measured.
c. Body weight will be recorded.
d. Medication compliance and concomitant medication will be assessed.
e. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).
f. Safety and efficacy parameters will be assessed as per Visit Schedule.
g. Adverse events will be recorded.
h. Urine pregnancy test will be performed for females of child-bearing potential.
i. Patients will be advised to maintain a stable lifestyle.

- **Visit 4 [Day 85 (+/- 7 Days)]**

a. Patients will undergo physical examination.
b. Vitals signs will be measured.
c. Body weight will be recorded.
d. Medication compliance and concomitant medication will be assessed.
e. ECG will be performed.
f. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).
g. Safety and efficacy parameters will be assessed as per Visit Schedule.

h. Adverse events will be recorded.
i. Urine pregnancy test will be performed for females of child-bearing potential.
j. Patients will be advised to maintain a stable lifestyle.

- **Visit 5 [Day 127 (+/- 7 Days)]**

a. Patients will undergo physical examination.
b. Vitals signs will be measured.
c. Body weight will be recorded.
d. Medication compliance and concomitant medication will be assessed.
e. Safety and efficacy parameters will be assessed as per Visit Schedule.
f. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).
g. Adverse events will be recorded.
h. Urine pregnancy test will be performed for females of child-bearing potential.
i. Patients will be advised to maintain a stable lifestyle.

- **Visit 6 [Day169 (+/- 7 Days)]**

a. Patients will undergo physical examination.
b. Vitals signs will be measured.
c. Body weight will be recorded.
d. Medication compliance and concomitant medication will be assessed.
e. ECG will be performed.
f. Liver biopsy will be performed to record final NAFLD Activity Score (Appendix 2).
g. Safety and efficacy parameters will be assessed as per Visit Schedule.
h. Adverse events will be recorded.
i. Serum pregnancy test will be performed for females of child-bearing potential.
j. Patients will be advised to maintain a stable lifestyle.

- **Visit 7 Follow-Up Visit [Day 197 (+/- 7 Days)]**

a. Patients will undergo physical examination.
b. Vitals signs will be measured.
c. Body weight will be recorded.
d. Concomitant medication will be assessed.
e. ECG will be performed.
f. Safety parameters will be assessed as per Visit Schedule.
g. Adverse events will be recorded.

Protocol Deviations:

During this study following will be considered as protocol deviations:

- Patients who did not meet entry criteria.
- Patients who received the wrong treatment or incorrect dose.
- Patients who received restricted medications.
- Patients with out of visit window assessments.
- IP non-compliance of <80% or >120%.

Subject Withdrawal Criteria:

1. Occurrence of a serious or intolerable AE and if considered in PI/Medical Expert's opinion that it is not in the subject's best interest to continue.
2. The Sponsor, IRB/IEC or PI or the regulatory terminates the study.
3. Either the PI or the Sponsor decides that discontinuing the study or discontinuing the subject is in the subject's best interest.
4. Any subject who wishes to withdraw his/her consent for participation in the study.
5. In case a subject becomes pregnant, then she will be withdrawn from the study.

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 an adverse event of Common Terminology Criteria for Adverse Event (CTCAE) of grade 3 or higher that is possible or likely drug related and discontinue any patient with an adverse event of 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.
    - 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 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 total bilirubin 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 $\geq$ 1.5 X ULN but < 5 X ULN, discontinue if ALT or AST increases to > 3 X baseline value
        - Discontinue if ALT or AST increase > 2 X baseline value AND the increase is accompanied by a concomitant total bilirubin level increase to > 2 X baseline value 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.

Concomitant Medication:

With the exception of excluded concomitant medications, other medications that subjects have been taking at stable dosages for at least 3 months prior to biopsy, i.e., statins, drugs for glycemic control and hypertension will be permitted as concomitant medications. To the extent possible, subjects 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 subject 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 Expert and Sponsor before being taken by the subject.

Restricted Medications:

- Drugs affecting insulin resistance (Glitazones/Glitazars/ GLP-1 agonists) will not be allowed during the study.
- Other drugs claimed for treatment of NASH (pentoxyphyllin, ursodeoxycholic acid, antioxidants such as vitamin E (>800 IU/day), glutathione, orlistat, betaine, incretin mimetics or non-prescribed complementary alternative medications (including dietary supplements, megadose vitamins, herbal preparations and special teas) will not be allowed during the study. *However, patients who are taking stable dose of Vitamin E for at least 3 months will be enrolled in the study.*
- Subjects 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.

No. of subjects in treatment arm:	Total 15 patients will be enrolled in this study.
Test product: **Dose:** **Mode of administration:**	Saroglitazar Magnesium 2 mg and 4 mg once daily (OD) Oral
Reference therapy: **Mode of administration:**	Placebo Oral, OD
Duration of treatment:	24 weeks

Criteria for efficacy	**Primary Endpoint:** The primary endpoint is to assess the changes in NAFLD Activity Score (NAS) at week 24 from baseline and with no worsening of fibrosis in NASH patients. **Secondary Endpoints:** From baseline to Week 24 : 1. To evaluate the percentage of responders in the treatment groups. *Responder is defined as a decrease from baseline of at least 2 points spread across at least 2 of the NAS components [steatosis, hepatocyte ballooning, and lobular inflammation] with no worsening of fibrosis.* 2. Percentage of responders defined by the disappearance of steatohepatitis. 3. Changes in the stage of steatosis, lobular inflammation and ballooning. 4. Changes in the stage of fibrosis. 5. Changes in the liver function tests. 6. Changes in the lipid profile. 7. Changes in the glycemic control and insulin resistance. 8. To assess the safety of Saroglitazar Magnesium 2 mg and 4 mg in patients with non-alcoholic steatohepatitis. *(Safety will be assessed during the study period through the reporting of AEs, by clinical laboratory tests, ECGs, vital sign, physical examination and body weight assessment at various time points during the study).*
Criteria for safety:	Safety endpoints include: • Frequency and severity of adverse events • Physical examination and body weight • Vital signs • Clinical laboratory testing (hematology, clinical chemistry, serology and urinalysis) • 12-lead electrocardiogram (ECG).

Statistical methods:

The demographic and baseline characteristics will be summarized. Subject disposition and reasons for withdrawal will be presented, as appropriate. Unless otherwise stated, all the continuous variables will be represented by n, mean, standard deviation, minimum, median and maximum. All the categorical variables will be presented as counts and percentages.

As this is a proof of concept (PoC) study no formal hypothesis testing will be done. All primary and secondary efficacy analysis will be summarised and analysed, appropriately, for modified Intent-To-Treat (mITT) and Per Protocol (PP) populations.

For safety analysis, all AEs observed during the study period will be listed. All AEs will be assessed for causality, severity and seriousness. The frequency and percentage of AE will be calculated and presented. The frequency tabulations of abnormal clinical laboratory values for the parameter will be presented by visit. Summary statistics for clinical laboratory findings and vital signs will be presented. A list of concomitant medications taken during the study period will be summarised.

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACO	Acyl CoA oxidase
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Co-variance
API	Active pharmaceutical ingredient
Apo	Apo Lipoprotein
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood count
cGMP	current Good Manufacturing Practices
CI	Confidence interval
CK	Creatinine kinase
CPK	Creatinine phosphokinase
CRA	Clinical research associate
CSR	Clinical Study Report
CYP	Cytochrome P450
CTCAE	Common Terminology Criteria for Adverse Event
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EDC	Electronic data capture
FA	Fatty acids
ECG	Electrocardiogram
FPG	Fasting plasma glucose
GGT	Gamma-glutamyl transferase
HbA1c	Glycosylated hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HepBsAg	Hepatitis B surface antigen
HepC Ab	Hepatitis C antibody
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOMA IR	Homeostasis model assessment for insulin resistance
ICD	Informed consent document
ICF	Informed consent form
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
INR	International normalized ratio
IP	Investigational Product
LDL	Low density lipoprotein
LFABP	Liver fatty acid binding protein
LFT	Liver function tests
LPL	Lipoprotein lipase
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
MTTP	Microsomal triglyceride transfer protein
NAFLD	Non-alcoholic Fatty Liver Disease

NAS	NAFLD Activity Score
NASH	Non-alcoholic Steatohepatitis
NYHA	New York heart Association
PPARs	Peroxisome proliferator-activated receptors
PP	Per-protocol
RFT	Renal function tests
RxR	Retinoid x receptor
SAE	Serious adverse event
SAM-e	S-adenosylmethionine
SD	Source documents
sdLDL	Small dense LDL
SMF	Site master file
SOPs	Standard operating procedures
TG	Triglyceride
TSH	Thyroid stimulating hormone
VLDL	Very low density lipoprotein
WBC	White blood cell

TABLE OF CONTENTS

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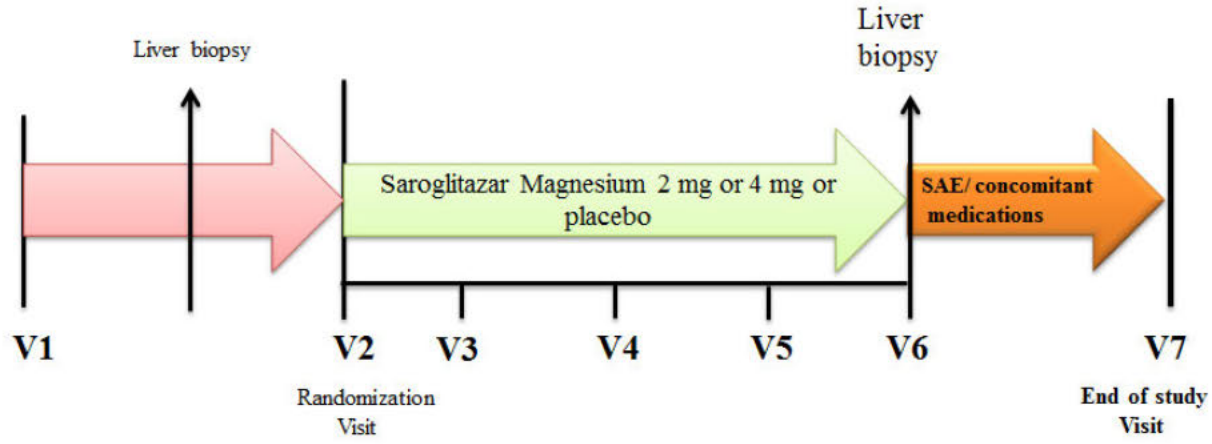
1 STUDY FLOW CHART



NOTE: Liver biopsy showing NASH within 6 months preceding Visit 1 can be used.

2 INTRODUCTION

2.1 MEDICAL BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by hepatic steatosis in the absence of a history of significant alcohol use or other known liver disease. Its progressive form is called Non-alcoholic steatohepatitis (NASH). This metabolic disorder occurs mainly in overweight or obese individuals, but recently NASH is emerging as one of the main causes of chronic liver disease. NASH is considered to be the hepatic component of the metabolic syndrome, which includes obesity, hyperinsulinemia, peripheral insulin resistance, diabetes, dyslipidemia and hypertension. NASH has been thought to be the precursor for many of the idiopathic liver cirrhosis. The pathogenic mechanism involves hyperinsulinemia and hepatic insulin resistance, hepatic fat accumulation (steatosis) and a "second hit" of oxidative stress producing inflammation and leading to fibrosis. But the actual succession of events in progression of NAFLD to NASH and cirrhosis is still poorly understood [1].

The general criteria for histological diagnosis of NASH generally include steatosis, hepatocyte injury in the form of ballooning and lobular inflammation. Hepatocyte injury can take the form of ballooning, apoptosis, or lytic necrosis. Ballooning is a major feature of NASH [2]. Furthermore ballooning has been associated with poor prognosis and severe ballooning has been correlated with higher incidence of cirrhosis [3]. Lobular inflammation is usually mild and consists of mixed inflammatory cells including lymphocytes, eosinophils and neutrophils. Scattered Kupffer cell aggregates are also common.

The prevalence of NAFLD and NASH has been major cause of liver disease worldwide. However, given the trends in the prevalence of diabetes and obesity, the prevalence of NAFLD and its consequences are expected to increase in the near future [4].

2.2 RATIONALE FOR CONDUCTING THE STUDY

With the increasing awareness and early recognition of asymptomatic patients with raised transaminases and the ongoing epidemic of the metabolic syndrome, NAFLD has become a common cause of referral to hepatology clinics. Recently there have been reports linking the development of hepatocellular carcinoma to NASH. In community studies, NAFLD correlates

with central adiposity, obesity, insulin resistance and the complications of insulin resistance-the metabolic syndrome and type 2 diabetes mellitus [3].

The prevalence of NAFLD and NASH has been major cause of liver disease worldwide. However, given the trends in the prevalence of diabetes and obesity, the prevalence of NAFLD and its consequences are expected to increase in the near future [4].

Very few trials have been conducted with drugs having definite therapeutic benefits in NASH and, as a consequence, no specific therapy has been approved for this condition. Metformin, thiazolidinediones, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, antioxidants, pentoxifylline, lipoprotein lipase activators, low caloric diets and exercise have been tested and repeatedly evaluated in order to estimate their efficiency, without any positive conclusion concerning their benefits. One study evaluating lifestyle modification for treatment of NASH improvements in liver enzymes, cholesterol and plasma hyaluronic acid levels [5]. This study used a lifestyle modification of encouragement to walk or jog for at least 30 minutes daily and a step 1 American Heart Association diet [6]. But controversy still exists over the optimal recognition, diagnosis and management of NASH, therefore treatment recommendations are still unclear [1, 7, 8, 12].

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

PPARα is central to hepatic lipid homeostasis. When hepatic fatty acid levels increase, PPARα is activated, leading to transcription of such genes as liver fatty acid binding protein (LFABP), acyl-CoA oxidase (ACO), cytochrome P450 (CYP)4A, microsomal triglyceride transfer protein (MTTP) and apolipoprotein B100 (apo B 100). The net effect is catabolism and clearance of fatty acids. It has recently been appreciated that the liver may respond to newly synthesized fatty acids differently from those 'recycled' from peripheral stores and this discrimination is mediated by selective effects on PPARα. This may explain why PPARα activation does not appear to occur as

an adaptive response in fatty liver disease, when it would be an effective pathway to enhance insulin sensitivity and suppress inflammatory recruitment. Thus, while pharmacologic PPARα activation effectively 'cured' fibrosing steatohepatitis in a murine, dietary model, the efficacy of such agents is less clear in humans. PPARγ is found predominantly in adipocytes. It has both opposite and complementary functions to PPARα. Thus, PPARγ activation leads to differentiation of adipocytes from pre-adipocytes *in-vitro*. This increases the lipid storage capacity of the adipose mass and in animals, also increases the number of small, insulin-sensitive adipocytes so as to improve insulin sensitivity. Increasingly, the importance of PPARγ is being recognized in the liver, despite the relatively low levels of expression normally found there. Steatosis is often associated with increased hepatocyte expression of PPARγ.

[redacted]

Therefore, a prospective, randomized, double-blind, placebo-controlled phase 2 study is designed to evaluate the safety and efficacy safety of Saroglitazar 2 mg and 4 mg in patients with NASH.

2.3 DRUG PROFILE

Saroglitazar, a dual PPAR agonist with predominantly PPARα and a moderate PPARγ agonist activity, [redacted]

Preclinical Experience

[redacted]

Clinical Experience

Saroglitazar Maximum Tolerated Dose in Phase 1 was 16 mg/day for 10 days and was found to be well tolerated. From preclinical studies and Phase I trial, it appeared that Saroglitazar had a promising safety and efficacy profile.

In Phase 1 study of healthy human volunteers, Saroglitazar was found to be well tolerated in single and multiple dose studies without any serious side effects [11].

A Phase 2 study was conducted to evaluate the efficacy and safety of Saroglitazar on the lipid and glucose profile in dyslipidemic patients with normal glucose tolerance, impaired glucose tolerance or diabetes.

[redacted]

A Phase 3 study was conducted to evaluate the efficacy and safety of Saroglitazar in diabetic dyslipidemic patients as compared to pioglitazone, there was significant reduction in the TG levels at all visits as compared to baseline. Similarly there were significant reductions in the very low density lipoprotein (VLDL) and total cholesterol levels as compared to pioglitazone. In another Phase 3 study of Saroglitazar in diabetic dyslipidemic patients not controlled with atorvastatin 10 mg revealed significant reduction in the TG levels as compared to placebo. Significant reduction in the low density lipoprotein (LDL) cholesterol, total cholesterol and apolipoprotein B levels with Saroglitazar 4 mg was observed as compared to baseline.

2.4 BENEFIT/RISK ASSESSMENT

Saroglitazar Magnesium 4 mg appeared to be an effective and safe in the treatment of NASH in a previously conducted Phase II trial. There were no persistent changes from baseline in various laboratory parameters, vital signs or electrocardiogram observed during the study period. [redacted] These events were mild and none of these events was considered clinically significant by the Investigator. There was neither body weight gain nor fluid retention. In addition there were no clinically significant increases in plasma creatinine level, which are some common PPARα-related side effects.

3 STUDY OBJECTIVES

To evaluate the safety and efficacy of Saroglitazar Magnesium 2 mg and 4 mg in patients diagnosed with non-alcoholic steatohepatitis (NASH).

3.1 PRIMARY OBJECTIVE

To evaluate the changes in NAFLD Activity Score (NAS) at week 24 from baseline and with no worsening of fibrosis in NASH patients.

3.2 SECONDARY OBJECTIVES

1. To evaluate the percentage of responders in the treatment groups.
2. To evaluate the percentage of responders, defined as the disappearance of steatohepatitis over the time period up to Week 24 in patients treated with Saroglitazar Magnesium 2 mg and 4 mg.
3. Changes from baseline to Week 24 in Saroglitazar Magnesium 2 mg and 4 mg for the following parameters:
    - Stage of steatosis, lobular inflammation and ballooning
    - Stages of fibrosis
    - Liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, direct bilirubin, total proteins and albumin).
    - Lipid profile parameters (triglyceride, small dense low density lipoprotein, high density lipoprotein, low density lipoprotein, very low density lipoprotein, total cholesterol and non HDL cholesterol Apo lipoprotein A1 and Apo lipoprotein B).
    - Insulin resistance and glycemic control parameters (fasting plasma glucose, glycosylated hemoglobin, fasting insulin, C-peptide, adiponectin, homeostasis model assessment beta and homeostasis model assessment for insulin resistance).

4. To assess the safety of Saroglitazar Magnesium 2 mg and 4 mg in patients with non-alcoholic steatohepatitis over 24 weeks of treatment.

4 STUDY POPULATION

Subjects clinically suspected of NASH and having laboratory evidence of abnormally elevated liver function tests (LFT) suggestive of NASH and confirmed histologically by biopsy will be recruited for the study. The histological evidence of NASH is defined as NAS ≥4 with a minimum score of 1 for all of its three components [steatosis, hepatocyte ballooning and lobular inflammation].

If the subject has consumed restricted medications but is otherwise considered eligible to be enrolled in this study by the Investigator, then a minimum of 1 month wash out period will be instituted before the screening visit.

4.1 NUMBER OF SUBJECTS PLANNED

A total 15 patients will be enrolled from a multiple centers in a ratio of 2:2:1 to have 6 patients in Saroglitazar Magnesium 2 mg, 6 patients in Saroglitazar 4 mg and 3 patients in placebo arm for 24 weeks.

4.2 INCLUSION CRITERIA

1. Patients able to provide written informed consent for participation in this trial.
2. Males or females, 18 to 75 years of age, both inclusive.
3. Female must be either of non-child bearing potential (surgically sterilized at least 6 months prior to screening or postmenopausal) or using one or more methods of contraception.
4. Histologic confirmation of NASH without cirrhosis (fibrosis stage 0, 1, 2, or 3) from liver biopsy performed either during the screening period or no more than 6 months prior to the first visit, with a NAS of ≥4 and a score of at least 1 in each (steatosis scored 0-3, ballooning scored 0-2 and lobular inflammation scored 0-3). If biopsy was performed within 6 months of screening, the slides, biopsy material or block should be available for baseline documentation. Such patients, whose historical biopsy report is available, should not use medications suspected of having an effect on NASH for at least 3 months prior to the screening.
5. BMI ≥25 kg/m^2.

6. For hypertensive patients, blood pressure must be controlled by a stable dose of antihypertensive medications for at least 3 months prior to screening (and the stable dose can be maintained throughout the study)
7. Patients with type 2 diabetes mellitus may be included if they fulfil the following criteria;
    a. Stable therapeutic regimen as defined by no changes in oral agents or dose for at least 3 months before screening and the stable dose can be maintained throughout the study.
    b. HbA1c $\leq$ 9.5%.
8. Patients agree to comply with the study procedure.

4.3 EXCLUSION CRITERIA

1. Pregnant and lactating female.
2. Positive pregnancy test.
3. Patients with history of myopathies or evidence of active muscle diseases.
4. Patients with history of alcohol consumption of >30 gm/day for men, >20 gm/day for women for consecutive previous 2 years and/or drug abuse.
5. Known allergy, sensitivity or intolerance to the study drug or formulation ingredients.
6. Participation in an interventional clinical study and/or receipt of any investigational medication within 3 months prior to screening.
7. History of malignancy in the past 5 years and/or active neoplasm with the exception of superficial, non-melanoma, skin cancer.
8. Any of the following laboratory values at screening:
    a. Direct bilirubin >1.5 mg/dL
    b. Serum albumin <2.5 g/dL
    c. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2
    d. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >200 IU/L
    e. Patients with international normalized ratio (INR) >1.5
    f. Creatinine kinase $\geq$ 1.5 ULN

g. Lipase ≥ULN
h. Amylase ≥ ULN.

9. Unstable cardiovascular disease, including:
    a. unstable angina, (i.e., new or worsening symptoms of coronary heart disease within the 3 months preceding screening), acute coronary syndrome within the 6 months preceding Screening, acute myocardial infarction within the 3 months preceding screening 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 screening
    b. history of (within 3 months preceding Screening) or current unstable cardiac dysrhythmias
    c. uncontrolled hypertension (systolic blood pressure [BP] > 155 mmHg and/or diastolic BP > 95 mmHg)
    d. Stroke or transient ischemic attack within the 6 months preceding screening.
10. Previous history of bladder disease and/or hematuria.
11. Previous liver biopsy that demonstrated presence of cirrhosis or radiologic imaging consistent with cirrhosis or portal hypertension.
12. Type 1 diabetes mellitus.
13. Use of drugs that are known CYP2C8 inhibitors/substrate.
14. Use of drugs associated with a clinical or histological picture consistent with fatty liver disease or NASH for more than 12 consecutive weeks in the 1 year prior to start of the study; (these include amiodarone, tamoxifen, methotrexate, glucocorticoids, anabolic steroids, tetracyclines, estrogens, valproate/valproic acid, chloroquine, anti-HIV drugs).
15. History of thyroid disease (hypothyroid patients who are euthyroid on thyroid hormone replacement can be included).
16. History of, or current, cardiac dysrhythmias.
17. History of bariatric surgery, or undergoing evaluation for bariatric surgery.
18. Patients with a >10% weight loss in the 3 months prior to screening.
19. 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, coronary artery disease, HIV or active gastrointestinal conditions that might interfere with drug absorption).

20. Patients on any treatment with other drugs used for treatment of NASH [pentoxyphyllin, ursodeoxycholic acid, antioxidants such as vitamin E (>800 IU/day), glutathione, orlistat, betaine, incretin mimetics or non-prescribed complementary alternative medications (including dietary supplements, megadose vitamins, herbal preparations and special teas)] or any medicine in clinical trials for NASH. *(However, patients who are taking stable dose of vitamin E for at least 3 months prior to screening will be enrolled in the study).*
21. History of other causes of chronic liver disease [autoimmune, primary biliary cirrhosis, hepatitis B virus (HBV) and hepatitis C virus (HCV), Wilson disease, alpha-1-antitrypsin deficiency, hemochromatosis etc.

4.4 SUBJECT WITHDRAWAL

Subjects may withdraw from the study at any time for any reason without prejudice to his or her future medical care. Although a subject 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 subject's rights. If there is a medical reason for withdrawal, the subject will remain under the supervision of the PI for follow-up of AE(s) as detailed in *Section 9.4.3*. Every effort will be made to continue clinical and/or laboratory follow-up, as appropriate, in subjects who wish to withdraw from the study drug) and reasonable efforts will be made to contact a subject who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health. A subject'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 subject.

As far as possible, all assessments scheduled for End-of-treatment must be performed on all subjects who receive the study drug but do not complete the study according to protocol. However, liver biopsy should be performed in those subjects who have completed at least 12 weeks of the study treatment.

4.4.1 Screen Failure

If a subject is termed as a screen failure for not meeting the inclusion/exclusion criteria, the subject may be rescreened only after obtaining Sponsor approval. The Sponsor may approve for rescreening those cases in which subjects failed the screening parameters within a narrow margin. Screening laboratory tests may be repeated following the approval of the Sponsor or its designee if the laboratory test results seem implausible or inaccurate.

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

4.5 DISCONTINUATION OF SUBJECTS FROM THE STUDY OR STUDY DRUG

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

1. Occurrence of a serious or intolerable AE and if considered in Investigator's/Medical Expert's opinion that it is not in the subject's best interest to continue.
2. The Sponsor, IRB/IEC or PI or the regulatory terminates the study.
3. Either the PI or the Sponsor decides that discontinuing the study or discontinuing the subject is in the subject's best interest.
4. The subject is lost to follow-up.
5. Any subject who wishes to withdraw his/her consent for participation in the study.
6. In case a subject becomes pregnant, then she will be withdrawn from the study.

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

A study completion CRF, which includes the reason for discontinuation, must be completed for all subjects who are discontinued from the study. If the subject is discontinued prematurely, the study completion CRF should clearly indicate the reason for discontinuation. If the subject

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 subject will be reported.

Every effort will be made to continue clinical and laboratory follow-up, as appropriate, in subjects who are withdrawn or in whom the study drug is stopped by the PI.

4.6 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 an adverse event of Common Terminology Criteria for Adverse Event (CTCAE) of grade 3 or higher that is possible or likely drug-related and discontinue any patient with an adverse event of 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.
    - 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 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 total bilirubin 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 ≥ 1.5 X ULN but < 5 X ULN, discontinue if ALT or AST increases to > 3 X baseline value
  - Discontinue if ALT or AST increase > 2 X baseline value AND the increase is accompanied by a concomitant total bilirubin level increase to > 2 X baseline value 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.

4.7 HANDLING OF SUBJECT WITHDRAWAL

In case of withdrawal of consent and unless otherwise stated by the subject in the withdrawal of consent, PI(s) will be encouraged to obtain information from the subject in order to follow the medical status of the subjects (especially when the subject withdraws his/her consent after having experienced an AE/SAE or an efficacy endpoint). Principal investigator or designee(s) must make reasonable attempts to contact subjects that are lost to follow-up, in order to obtain health status and reason for withdrawal. These attempts must be documented in the medical records.

5 STUDY TREATMENTS/INVESTIGATIONAL PRODUCT (IP) MANAGEMENT

Saroglitazar Magnesium 2 mg or 4 mg or placebo tablet will be administered in patients with NASH, once daily in the morning before breakfast for a period of 24 weeks.

5.1 TREATMENTS TO BE COMPARED

5.1.1 Investigational Product Description

The investigational products (IPs) that will be used in this study are outlined in Table 2.

Table 2 Identity of Study Drugs

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

[redacted]

5.1.2 Comparator Drug Description

Placebo will be used as comparator, which will be formulated as tablets, and will contain above mentioned excipients without Saroglitazar Magnesium [redacted] The IP will be manufactured following current-Good Manufacturing Practice (cGMP) guideline.

5.2 DOSAGE AND TREATMENT SCHEDULE

Subjects will receive either Saroglitazar Magnesium 2 mg or 4 mg or placebo orally once each morning before breakfast for a period of 24-week.

However, on the day of the scheduled clinical visit, subjects will have the IP administered on site after fasting blood sample collection. If on the day of a scheduled clinic visit the subject has already taken the IP, all procedures except blood sample collections will be performed. The subject will be asked to return the next day to have the blood sample collected, and will be reminded not to take the IP until after the blood sample collections. If the subject again returns

having taken the IP, blood samples will be collected and the subject will be asked to return for the next scheduled visit.

5.3 PACKAGING, LABELLING AND SUPPLY

Study drugs will be packed, labelled and supplied by the Sponsor according to all local regulatory requirements. [redacted]. The PI or designee will confirm the receipt of IP in writing via fax/email.

[redacted]

Unused drug supplies will be returned to the Sponsor (or designee) for destruction/ destroyed at the site after approval for the same by the Sponsor. No study drug will be destroyed or returned until complete drug accountability has been performed by the study monitor. All supplies must be accounted for at the end of the study period.

At the time of or in proximity to the site initiation, each Investigator will be provided sufficient supply of study drug. Investigational product must be dispensed to each subject in such a way that the subject can take the doses in accordance with the Protocol. A drug accountability log(s) for recording the receipt, dispensing and return of the IP must be maintained by the PI or any designated personnel. The drug accountability log(s) must be kept up to date and must be made availability to the study monitor during monitoring visits.

A temperature log must be maintained that the drug supplies are stored at the correct temperature throughout the study period.

5.4 STORAGE CONDITIONS

Investigational products will be stored at room temperature (20°C to 25°C or 68°F to 77°F) in a dry place away from light at the study site or pharmacy. If the IP temperature extends outside the

20-25°C range, a temperature excursion must be documented in the study-specific temperature log , and sent to the Sponsor. If the excursion is within 15-30°C, quarantine is not required, and the IP is acceptable for use. If the excursion is outside of the 15-30°C range, the IP must be quarantined until a decision on the stability of the IP is made by the Sponsor. If the excursion goes beyond the range of $15\text{-}30^0$ C it will be considered as a protocol deviation. Protect the IP from light. All IP supplies in the study will be stored in a secure location with access limited to the Site Pharmacist or the PI designated site staff.

5.5 BLINDING/UNBLINDING

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

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

The blinding must only be broken following a discussion on a case-by-case basis, at the discretion of the Sponsor/Medical Expert. If an emergency unblinding becomes necessary, the PI should notify the Sponsor/Medical Expert, if possible, before unblinding. If it is determined that unblinding is necessary, a scratch card/blinding envelop will be decoded to reveal the treatment received by the patient. All cases resulting in an unblinding event will be documented and reported to the Medical Expert and the Sponsor. If the blind is broken, the date, time and reason must be recorded in the patient's eCRF/source document 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, all data queries have been resolved, and the assignment of patients to the analysis sets has been completed.

5.6 METHOD OF ASSIGNING SUBJECT TO TREATMENT GROUP

Patients will be randomly assigned in a 2:2:1 ratio to Saroglitazar Magnesium 2 mg or 4 mg or placebo. The block randomization schedule will be generated using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA)..

5.7 SELECTION OF DOSES

Saroglitazar Magnesium 1 mg, 2 mg and 4 mg have favorably modified the lipid profile in the dyslipidemic patients during its development in Phase II and III studies. Based on the safety and efficacy results of Saroglitazar Magnesium, it was approved in India at the doses of 2 mg and 4 mg QD for the treatment of "Diabetic Dyslipidemia" and "Hypertriglyceridemia with T2DM not controlled by statin therapy". Based on these results, Saroglitazar Magnesium 2 mg and 4 mg doses have been selected for this study.

5.8 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

5.8.1 Previous and Concomitant Medications

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

5.8.2 Restricted Concomitant Medications

Drugs affecting insulin resistance (Glitazones/Glitazars/GLP-1 agonists) will not be allowed during the study.

Other drugs claimed for treatment of NASH (pentoxyphyllin, ursodeoxycholic acid, antioxidants such as vitamin E (>800 IU/day), glutathione, orlistat, betaine, incretin mimetics or non-prescribed complementary alternative medications (including dietary supplements, megadose vitamins, herbal preparations and special teas) will not be allowed during the study. *However, patients who are taking stable dose of Vitamin E for at least 3 months will be enrolled in the study.*

Subjects 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.

5.8.3 Permitted Concomitant Medications

With the exception of excluded concomitant medications, other medications that subjects have been taking at stable dosages for at least 3 months prior to biopsy, i.e., statins, drugs for glycemic control and hypertension will be permitted as concomitant medications. To the extent possible, subjects 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 subject 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 Expert and Sponsor before being taken by the subject.

5.8.4 Other Restrictions

5.8.4.1 Alcohol

Subjects are encouraged to stop alcohol consumption entirely during the study. 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.

5.8.4.2 Diet and Exercise

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

5.9 OVER DOSE AND DRUG INTERACTION

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

[redacted]

5.10 TREATMENT COMPLIANCE

The patients will be asked to bring their bottles of the IP to the next visit; compliance for dosing will be assessed by examination of the bottles and tablet count by study personnel and documentation on Individual drug accountability log(s). 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 acceptable.

6 OBSERVATIONS

6.1 CRITERIA FOR SAFETY

6.1.1 Safety Variables

The following safety assessments are conducted to evaluate the safety:

- Frequency and severity of adverse events
- Physical Examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities and the neurological and musculoskeletal systems.
- Body weight
- Vital Signs
- Clinical laboratory testing (hematology, clinical chemistry, serology and urinalysis).
- 12-lead electrocardiogram (ECG).

6.1.2 Medical History and Demographic Information

The medical history comprises:

- General medical history
- Medication history
- Reproductive history.

The following demographic information will be recorded:

- Gender
- Age
- Ethnic origin
- Race
- Height
- Body weight
- Body mass index.

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 1). Safety laboratory variables are listed in Table 4.

Table 4 Safety Laboratory Assessments

Hematology	Complete blood count, hemoglobin, PT, INR. Electrolytes (sodium, potassium, chloride and bicarbonate)
Clinical chemistry	**LFT:** ALT, AST, ALP, total bilirubin, GGT, total proteins and albumin. Amylase and lipase **RFT:** Serum creatinine, blood urea nitrogen, eGFR **Cardiac marker**: CK **Lipid Panel and lipoprotein:** TG, sdLDL, LDL, VLDL, HDL, total cholesterol, non HDL cholesterol, Apo A1 and Apo B **Glycemic control:** Fasting plasma glucose, HbA1c TSH
Urinalysis	**Urine Chemical Examinations:** pH, specific gravity, protein, glucose, bilirubin, urobilinogen, ketone bodies and nitrite **Urine Microscopy:** epithelial cells, RBCs, pus cells, cast and crystals
Serology	HIV type 1 and type 2 HAV IgM HBsAg HCV
Pregnancy test	Serum pregnancy test and urine pregnancy test for females of child-bearing potential

AST = aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; BUN = blood urea nitrogen; CK = creatinine kinase; eGFR = estimated Glomerular Filtration Rate; GGT = γ-glutamyl transferase; HAV IgM= anti hepatitis A virus; HbA1c = Glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; HIV = human immunodeficiency virus; INR = international normalized ratio; LDL = low-density lipoprotein; PT = Prothrombin time; sdLDL = Small dense low density lipoprotein; RBC = Red blood cell, sdLDL = Small dense low density lipoprotein; TSH = Thyroid stimulating hormone; VLDL = very low density lipoprotein.

6.1.3.2 Urine Tests

Urine pregnancy test (females of child-bearing potential only at Visits 2, 3, 4, 5) will be processed by a local laboratory.

6.1.3.3 Vital Signs

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

- Sitting blood pressure (systolic and diastolic; mmHg)

- Pulse (beats per minute)
- Oral body temperature (°F)
- Respiratory rate (breaths per minute).

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

6.1.3.4 Twelve-lead Electrocardiograms

Electrocardiograms will be performed locally at the study site in accordance with the Schedule of Assessments (Table 1). Subjects should be in resting position for 5 minutes before ECG recording and performed before any blood draw that occurs at the same visit.

6.1.3.5 Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Assessments (Table 1). Patients' body weight will be recorded during all physical examinations. Height will be recorded at Screening Visit only).

6.2 EFFICACY

6.2.1 Primary Endpoint

The primary endpoint is to assess the changes in NAFLD Activity Score (NAS) at week 24 from baseline and with no worsening of fibrosis in NASH patients.

6.2.2 Secondary endpoints

From baseline to Week 24:

1. To evaluate the percentage of responders in the treatment groups.

   Responder is defined as a decrease from baseline of at least 2 points spread across at least 2 of the NAS components [steatosis, hepatocyte ballooning, and lobular inflammation] with no worsening of fibrosis.
2. Percentage of responders, defined by the disappearance of steatohepatitis.
3. Changes in the stage of steatosis, lobular inflammation and ballooning.
4. Changes in the stage of fibrosis.

5. Changes in the liver function tests.
6. Changes in the lipid profile.
7. Changes in the glycemic control and insulin resistance.
8. To assess the safety of Saroglitazar Magnesium 2 mg and 4 mg in patients with non-alcoholic steatohepatitis.

(Safety will be assessed during the study period through the reporting of AEs, by clinical laboratory tests, ECGs, vital sign, physical examination and body weight assessment at various time points during the study).

6.2.3 Blood Samples

Multiple venipunctures should be avoided to collect blood samples. It is recommended to collect blood sample for safety and efficacy measurement at a given visit.

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

- Liver function tests include ALT, AST, ALP, direct bilirubin, GGT, total proteins and albumin.
- Lipid parameters and lipoproteins include LDL, sdLDL, VLDL, HDL, triglyceride, total cholesterol, non HDL cholesterol, and Apolipoprotein A1, Apolipoprotein B.
- Glycemic control includes FPG, fasting insulin, adiponectin, C-peptide, HOMA IR, HOMA beta and HbA1c.

6.2.4 Total Amount of Blood

The total amount of blood drawn from each subject over the study will not exceed 500 mL.

6.3 APPROPRIATENESS OF MEASUREMENT

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

6.4 ABNORMAL LABORATORY FINDINGS

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

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

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

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

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

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

7 INVESTIGATIONAL PLAN

7.1 STUDY DESIGN AND PLAN

This is a randomized, double-blind, placebo-controlled, study to evaluate safety and efficacy of Saroglitazar Magnesium 2 mg and 4 mg in patients with NASH. This study will be initiated after obtaining the approvals of Institutional Ethics Committee/Institutional Review Board (IEC/IRB) and the local Regulatory Authority.

It is the responsibility of the Principal Investigator (PI) to ensure that the study is conducted in accordance with the protocol, International Council for Harmonisation Good Clinical Practice, and all applicable regulatory requirements. Informed consent will be obtained before the start of any study related procedures.

As per the contemporary guidelines, the PI shall maintain Source Documents (SD), Site Master File (SMF), Informed Consent Forms/Documents (ICF/ICD) and other logs/forms during the conduct of a study.

All laboratory reports should be reviewed by the PI and/or his/her designee and any abnormal findings should be addressed. All protocol deviations occurring on the study shall be documented and the Sponsor and IEC/IRB informed.

Patients clinically suspected of NASH will be invited for a screening programme for inclusion in the study. Patients will be screened according to the inclusion and exclusion criteria. Clinical evaluation will be conducted for baseline characteristics and anthropometry measurements such as body weight and height.

After clinical evaluations, all baseline safety and efficacy parameters will be recorded as per Table 1. All laboratory collections will be performed following overnight fasting (at least 8 hrs).

Following confirmation of all clinical and laboratory inclusion and exclusion criteria, patients will continue into the screening period. During the screening period liver biopsy will be performed. However, if a biopsy was performed within 6 months the slides and biopsy material, or block, must be made available for baseline documentation. Such Patients, whose historical biopsy report is available, should not use medication suspected of having an effect on NASH from the 3 months prior to the screening.

If the patient has consumed restricted medications but is otherwise considered eligible to be enrolled into this study by the PI, a minimum of 1 month wash out period would be instituted before the screening visit.

Liver biopsy will be performed to confirm the diagnosis of NASH and record a baseline NAFLD Activity Score (Appendix 2). The histological evidence of NASH is defined as NAS $\geq$ 4 with a minimum score of 1 for all of its three components [steatosis, hepatocyte ballooning, and lobular inflammation].

Following confirmation of inclusion/exclusion criteria and upon histological confirmation of NASH by liver biopsy, patients will be enrolled into the study.

Eligible patients will be randomly assigned to receive Saroglitazar Magnesium 2 mg or 4 mg or placebo in a 2:2:1 ratio for 24 weeks.

Upon completion of 24 weeks of treatment, liver biopsy will be performed and the NAFLD Activity Score recorded (Appendix 2).

The scheduled visits during this study will be as follows:

- Visit 1: Screening Visit [-4 Week (-28 Days)],
- Visit 2: Enrollment Visit (Day 1± 7 Days/Week 0),
- Visit 3: Day 43/Week 6 ± 7 Days,
- Visit 4: Day 85/Week 12 ± 7 Days,
- Visit 5: Day 127/Week 18 ± 7 Days,
- Visit 6: Day 169/Week 24 ± 7 Days,
- Visit 7: Follow-up Visit: Day 197/Week 28 ± 7 Days,

Patients will be advised to follow a stable lifestyle. No change in the intensity of lifestyle (Diet/Exercise) will be allowed during the period of study. Patients will be monitored for safety and efficacy parameters as per Table No 1.

If further investigations are required in case of any AE, Investigator is advised to assess the AE and take necessary action, if required. Patients are advised to contact the Investigator for any complaints.

7.2 STUDY PROCEDURES AT EACH VISIT

Visit Schedule

- **Screening Visit 1 [Week -4 (-28 days)]**

a. All patients will be required to sign and date the IRB/IEC approved ICF after all study-related procedures have been explained by the PI/designee and understanding the contents.

b. The informed consent process will be documented in the Source Documents, ICF and other relevant logs and signed and dated by the Investigator or delegated study team members on site. Prior to subject participation in the study, written informed consent will be obtained from each subject according to the regulatory and legal requirements of the participating country, including state-specific requirements.

c. Patients will be screened for eligibility; those qualifying will be invited to participate in the study.

d. Demographics, vitals, physical examination, medical history, prior and concomitant medication review will be recorded.

e. Clinical evaluation will be done for baseline characteristics and body weight will be recorded.

f. After clinical evaluations, all baseline safety and efficacy parameters will be assessed as per Table 1. All laboratory investigations will be performed on overnight fasting blood samples. Electrocardiograph (ECG) will be performed.

g. Serum pregnancy test will be done for females of child-bearing potential.

h. Patients are advised to maintain a stable life-style.

i. Adverse events will be recorded.

Liver biopsy Visit

a. Liver biopsy will be done after the patient passes all other inclusion and exclusion criteria to confirm NASH diagnosis and record a baseline NAFLD Activity Score (Appendix 2). If biopsy is done within 6 months, the slides, biopsy material or block should be available for baseline documentation. Such patients, whose historical biopsy

report is available, should not use medication suspected of having an effect on NASH from the 3 months prior to the Screening.

b. Liver biopsy will be performed with a 16 gauge (1.6 mm) needle with Ultrasound guidance. The length of the specimen collected should be approximately 1.5 cm. The specimen will be read centrally for NAFLD Activity Score by pathologist at Virginia Commonwealth University, Medical Center, 1250 E Marshall St Richmond, VA 23298 United States.

- **Visit 2 Enrollment Visit [Week 0, Day 1+/- 7 Days]**

a. Patients satisfying the inclusion and exclusion criteria will be randomly assigned to receive Saroglitazar Magnesium 2 mg or 4 mg or placebo.
b. Patients will undergo physical examination.
c. Concomitant medications will be assessed.
d. Vitals signs will be recorded.
e. Body weight will be recorded.
f. ECG will be performed.
g. Adverse events will be recorded.
h. Urine pregnancy test will be performed for females of child-bearing potential.
i. Safety and efficacy parameters will be assessed as per Table 1.
j. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).
k. Patients are advised to maintain a stable life-style.

- **Visit 3 [Day 43 (+/- 7 Days)]**

a. Patients will undergo physical examination.
b. Vitals signs will be measured.
c. Body weight will be recorded.
d. Medication compliance and concomitant medication will be assessed.
e. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).
f. Safety and efficacy parameters will be assessed as per Table 1.
g. Adverse events will be recorded.

h. Urine pregnancy test will be performed for females of child-bearing potential.

i. Patients will be advised to maintain a stable lifestyle.

- **Visit 4 [Day 85 (+/- 7 Days)]**

a. Patients will undergo physical examination.

b. Vitals signs will be measured.

c. Body weight will be recorded.

d. Medication compliance and concomitant medication will be assessed.

e. ECG will be performed.

f. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).

g. Safety and efficacy parameters will be assessed as per Table 1.

h. Adverse events will be recorded.

i. Urine pregnancy test will be performed for females of child-bearing potential.

j. Patients will be advised to maintain a stable lifestyle.

- **Visit 5 [Day 127 (+/- 7 Days)]**

a. Patients will undergo physical examination.

b. Vitals signs will be measured.

c. Body weight will be recorded.

d. Medication compliance and concomitant medication will be assessed.

e. Safety and efficacy parameters will be assessed as per Table 1.

f. A 6-week supply of investigational product will be dispensed (42 tablets + 7 tablets for one week allowance).

g. Adverse events will be recorded.

h. Urine pregnancy test will be performed for females of child-bearing potential.

i. Patients will be advised to maintain a stable lifestyle.

- **Visit 6 [Day169 (+/- 7 Days)]**

a. Patients will undergo physical examination.

b. Vitals signs will be measured.

c. Body weight will be recorded.

d. Medication compliance and concomitant medication will be assessed.

e. ECG will be performed.

f. Liver biopsy will be performed to record final NAFLD Activity Score (Appendix 2).

g. Safety and efficacy parameters will be assessed as per Table 1.

h. Adverse events will be recorded.

i. Serum pregnancy test will be performed for females of child-bearing potential.

j. Patients will be advised to maintain a stable lifestyle.

- **Visit 7 Follow-Up Visit [Day 197 (+/- 7 Days)]**

a. Patients will undergo physical examination.

b. Vitals signs will be measured.

c. Body weight will be recorded.

d. Concomitant medication will be assessed.

e. ECG will be performed.

f. Safety parameters will be assessed as per Table 1.

g. Adverse events will be recorded.

7.3 ADHERENCE TO PROTOCOL

The PI and the site staff shall strictly adhere to the protocol and GCP guidelines. All patients will be strictly required to follow the instructions given to them as per this protocol. For any deviation or violation from protocol, considered serious, the patient may be withdrawn from the study at the discretion of the Sponsor or the PI.

7.4 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 periodic reports from the EDC. The formal structure and conduct of DMC will be according to a previously agreed upon remit.

7.5 PROTOCOL DEVIATIONS

For the purpose of this study, no distinction will be made between Protocol Violations and Deviations. Deviations will be categorized as Clinical Study Report (CSR) non-reportable protocol deviations and as CSR reportable protocol deviations. A CSR non-reportable protocol deviation includes any deviations that do not necessarily influence the results/outcome of

primary endpoints or patient safety. A CSR non-reportable protocol deviation does not require immediate notification to the IRB/IEC unless otherwise specified by IRB/IEC requirements. All CSR non-reportable protocol deviations will be noted in monitoring reports and provided to the PI by monitor, if required.

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

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

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

The clinical study report will provide the list of protocol deviations in a separate section. The result will be analysed for all participants with CSR reportable protocol deviations.

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

- Patients who did not meet entry criteria.
- Patients who received the wrong treatment or incorrect dose.
- Patients who received restricted medications.
- Failure to report within specified time lines of the planned visits.
- IP non-compliance of <80% or >120%.

7.6 ADJUDICATION

An external independent Central Adjudication Committee (CAC) will adjudicate serious adverse events (SAEs), including all deaths, that are known or suspected to be a Major Adverse Cardiac Events (MACE) or heart failure hospitalizations. The CAC members will be independent of the

Sponsor, the 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 BIOSTATISTICS

8.1 STATISTICAL DESIGN

Statistical analysis will be performed on efficacy variables.

As this is a proof of concept (PoC) study no formal hypothesis testing will be done. All primary and secondary efficacy analysis will be summarised and analysed, appropriately, for modified Intent-To-Treat (mITT) and Per Protocol (PP) populations. The PP population will consist of all randomized patients completing the treatment phase (has taken ≥80% and ≤120% of the study drug) as per the study protocol and do not have any CSR reportable protocol deviation in such a way that could affect efficacy outcome. The mITT population will consist of all randomized patients who have taken at least one dose of the study treatment and have at least one post-baseline efficacy data. Last observation carried forward method will be used as an imputation method for post-baseline missing values for mITT analysis.

8.2 PLANNED ANALYSIS

8.2.1 Populations

8.2.1.1 Safety population

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

8.2.1.2 Modified intention-to-treat population (mITT)

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

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

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

8.2.1.3 Per-protocol population (PP)

The per-protocol population (PP) includes:

1. All enrolled patients who meet all the eligibility criteria.

2. Completed the study in compliance with the protocol.
3. Do not have any CSR reportable protocol deviation that affects the evaluation of the efficacy endpoints.

8.2.2 Statistical Analysis

As this is a proof of concept (PoC) study no formal hypothesis testing will be done.

All primary and secondary efficacy analysis will be summarised and analysed, appropriately, for modified Intent-To-Treat (mITT) and Per Protocol (PP) populations.

Change and percentage change for primary and secondary efficacy endpoints (continuous data) will be calculated as follows:

Change from baseline to Week 24 will be determined as (Week 24 - Baseline) and

Percentage change from baseline will be determined as [(Week 24 - Baseline)/Baseline]*100.

All primary and sceondary endpoints will be summarized as: n, mean, standard deviation, median, minimum and maximum for continuous variables; count and percentage for categorical variables at each visit.

8.2.3 Safety Analysis

All safety analysis will be carried out on the safety population. The frequency tabulations of abnormal clinical laboratory values for the parameter will be presented by visit. Summary statistics for clinical laboratory parameters, ECG, physical examination and vital signs will be presented by visit.

All AEs observed during the study period will be listed. Incidence of all AEs reported during the study will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) (version 19 or higher) by body system, frequency, severity, seriousness and relationship to study drug and expectedness. Frequency and percentage of AEs occur during the course of study will be calculated and presented in the report. All AEs will be assessed for causality, severity and seriousness. The frequency tabulations of abnormal clinical laboratory values for the parameter will be presented by visit. Summary statistics for clinical laboratory findings and vital signs will be presented.

8.2.4 Demographic and Baseline Characteristics

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

8.2.5 Interim Analysis

No interim analysis will be performed.

8.2.6 Handling of Missing Data

Clarifications, wherever possible, will be obtained from the PI or designee for any missing data or for any illegible entry, unused or unauthenticated data.

Patients who are discontinued from the study will be excluded from PP analysis set. Any enrolled patient who are discontinued from the study for any reason and have at least one post-baseline efficacy measurement will be included in the mITT analysis set. LOCF method will be used as an imputation method for post-baseline missing values in mITT population set.

8.3 RANDOMIZATION

Patients will be randomly assigned in a 2:2:1 treatment allocation ratio to Saroglitazar Magnesium 2 mg and 4 mg and placebo, respectively. The randomization schedule will be generated to ensure the treatment balance by using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA).

8.4 DETERMINATION OF SAMPLE SIZE

This proof of concept study will include total 15 patients receiving from a multiple centers in a ratio of 2:2:1 to have 6 patients in Saroglitazar Magnesium 2 mg, 6 patients in Saroglitazar 4 mg and 3 patients in placebo arm for 24 weeks.

9 ADMINISTRATIVE MATTERS

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

9.1 ETHICS

9.1.1 Institutional Committee Review and Communications

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

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

9.1.2 Informed Consent and Subject Information

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

PI or designee as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally authorised representative.

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

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

9.2 DATA MANAGEMENT AND RECORD KEEPING

9.2.1 Drug Accountability

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

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

9.2.2 Data Management

9.2.2.1 Data Handling

Data will be recorded by the PI or designee into eCRFs and reviewed by the study monitor during monitoring visits. The study monitor will verify data recorded in the electronic data capture (EDC) system against source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect and/or inconsistent data has been accounted for and the eCRF is signed by the PI.

9.2.2.2 Computer Systems

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

9.2.2.3 Data Entry

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

9.2.2.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

9.2.2.5 Data Validation

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

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

9.2.3 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the PI's site. Data reported on the eCRFs must be consistent with the source documents or the discrepancies must be explained.

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

The following data to be reported on the eCRF should be included and derived from source documents:

1. Subject identification (subject number, gender, date of birth/age)
2. Subject participation in the study (subject number, date informed consent given)
3. Dates of subject's visits
4. Medical history
5. Medication history
6. AEs (onset and end)
7. SAEs (onset and end)
8. Originals or copies of laboratory results: All laboratory reports must be reviewed by the Investigator and/or his/her designee; any abnormal findings should be addressed.
9. Conclusion of patient's participation in the study.

9.2.4 Direct access to Source Data/Documents

The PI/ Institution will permit study-related monitoring, audits, IRB/IEC reviews and regulatory inspections by providing direct access to all related source data/documents. Case report forms and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor(s), auditor(s) and inspection by applicable regulatory authorities. The on-site monitor will review all eCRFs and ICFs. The accuracy of the data will be verified by reviewing the documents described in *Section 9.2.3*.

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

9.2.5 Trial Monitoring

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

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

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

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

9.3 QUALITY AUDITS

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

9.4 PROCEDURES

9.4.1 Adverse Events

All AEs occurring during the course of the clinical study from the signing of the informed consent onwards will be collected, documented and reported to the Sponsor by the PI or designee according to the specific definitions and instructions detailed in this section. The Common Terminology Criteria for Adverse Event (CTCAE) (Version 4.03 or higher) system will be used for reporting and grading AEs.

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

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

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

9.4.2 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

1. Results in death;
2. Is life threatening;
3. Results in persistent or significant disability/incapacity;
4. Results in inpatient hospitalization or prolongs an existing inpatient hospitalization;

5. Is a congenital anomaly/birth defect;
6. Is another important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse event reporting-procedures for Investigator:

Initial Reports:

Any SAE, or follow-up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 7 days following cessation of treatment, whether or not related to the Sponsor's product, must be reported to the Sponsor within 24 hours of the knowledge of the occurrence to investigational site.

Additionally, any SAE, considered by the PI or designee, who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the PI or designee at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

Safety Contact Information:

[redacted]

Follow-Up Reports

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

9.4.3 Follow-up of Adverse Events

All AEs experienced by a subject, 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 PI and Medical Expert, until there is a satisfactory explanation for the changes observed, until the subject is lost to follow-up or until the subject has died.

9.4.4 Evaluating Adverse Events

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

9.4.4.1 Severity

The PI or designee will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's eCRF. The Common Terminology Criteria for Adverse Event (CTCAE) (Version 4.03 or higher) system will be used for reporting and grading AEs severity of events not classified in CTCAE will be assessed according to the following scale:

Mild: Event is usually transient and easily tolerated, requiring no special treatment and causing no disruption of the subject's normal daily activities.

Moderate: Event introduces a low level of inconvenience or concern to the subject 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 subject's normal daily activities and generally requires systemic drug therapy or other treatment. Severe events are usually incapacitating.

9.4.4.2 Causality

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

Causal relationship will be classified according to the following criteria:

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

9.4.4.3 Outcome

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

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

9.4.5 Expected Adverse Events

Adverse events reported by 2% or more subjects treated with Saroglitazar Magnesium during the double-blind, active-controlled study with Pioglitazone as the comparator regardless of causality

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

9.4.6 Pregnancy

At the Screening Visit, Visit 6 and Visit 7, every female subject of child-bearing potential will be tested for serum pregnancy test. Urine pregnancy test will be performed at Visit 2, 3, 4 and Visit 5. Women are advised not to become pregnant during the study and for at least 4 weeks ± 7 days after the end of the treatment period. Adequate contraceptive measures shall be used to prevent pregnancy. Even when contraceptive methods are used, there is a small risk that pregnancy might occur. In case a patient becomes pregnant, then she will be withdrawn from the study and adequate monitoring of the patients will be conducted.

Although pregnancy and lactation are not considered adverse events, it is the responsibility of the PI or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them) that occurs during the study or within 4 weeks of completing the study. All patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

9.5 RULES FOR AMENDING PROTOCOL

All amendments must be documented, dated and signed by all signatories (or their successors) of the original protocol and then will be submitted to Regulatory Authorities/IEC/IRB.

Modification only for logistical or administrative changes may be implemented immediately; however, both the IEC/IRB and the Regulatory Authority will be notified.

9.6 FINANCIAL DISCLOSURE

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

9.7 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

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

9.8 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions of participating physicians, and site personnel, the Sponsor's representatives, Monitor, Auditor, to the IRB or IEC and the regulatory health authorities as required under the law. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

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

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

9.9 FINAL REPORT AND PUBLICATION POLICY

A report will be prepared under the responsibility of the PI and according to the standards of the Sponsor. It will include the tabulated data and the biostatistical report on the data.

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

9.10 ARCHIVING

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

10 REFERENCES

1. Georgescu EF; Georgescu, M. Therapeutic Options in Non-Alcoholic Steatohepatitis (NASH). Are all Agents Alike? Results of a Preliminary Study. *J Gastrointestin Liver Dis*. 2007:16(1);39-46.
2. Naga Chalasani, Zobair Younossi, Joel E. Lavine, Anna Mae Diehl, Elizabeth M. Brunt, Kenneth Cusi, Michael Charlton, Arun J. Sanyal. 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): 2005-2023.
3. Kleiner et al. Design and Validation of a Histological Scoring System for Nonalcoholic Fatty Liver Disease. *Hepatology*. 2005:41(6);1313-1321.
4. Jorge A et al. Assessment of treatment response in Non-Alcoholic steatohepatitis using advanced magnetic resonance imaging. *Annals of Hepatology*. 2014:13 (2): 166-178.
5. Kugelmas et al. Cytokines and NASH: A Pilot Study of the Effects of Lifestyle Modification and Vitamin E *Hepatology*. 2003;38:413-419.
6. Krauss et al., AHA Dietary Guidelines: Revision 2000: A Statement for Healthcare Professionals From the Nutrition Committee of the American Heart Association *Circulation*. 2000;102:2284-2299.
7. Ibrahim et al., Nonalcoholic fatty liver disease: current and potential therapies. *Life Sci*. 2013;92(2):114-8.
8. Arun J. Sanyal, Elizabeth M. Brunt, David E. Kleiner, Kris V. Kowdley, Naga Chalasani, Joel E. Lavine, VladRatziu and Arthur McCullough. Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis. *Hepatology*. 2011;54:344-353.
9. Pai V, Paneerselvam A, Mukhopadhyay S, Bhansali A, Kamath D, Shankar V, Gambhire D, Jani RH, Joshi S, Patel P (2014) A Multicenter, Prospective, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4 mg Compared to Pioglitazone 45 mg in Diabetic Dyslipidemia (PRESS V). J Diabetes Sci Technol. DOI: 10.1177/1932296813518680
10. Jani RH, Pai V, Jha P, Jariwala G, Mukhopadhyay S, Bhansali A, Joshi S. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of

saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). Diabetes Technology & Therapeutics. 2014;16(2): DOI: 10.1089/dia.2013.0253.

11. Jani RH, Kansagra K, Jain M, Patel H: Pharmacokinetics, safety and tolerability of saroglitazar (ZYH1), a predominant PPARα agonist and moderate γ agonist activity in healthy human subjects. Clin Drug Investig 2013;33:809-816.
12. Claudia Filozof, Barry J. Goldstein, Richard N. Williams, Arun Sanyal. Non-Alcoholic Steatohepatitis: Limited Available Treatment Options but Promising Drugs in Development and Recent Progress Towards a Regulatory Approval Pathway. Drugs 2015;75:1373–1392.
13. Galgani J, Ravussin E. Energy metabolism, fuel selection and body weight regulation. Int J Obes. 2008;32:S109-S119.
14. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use ICH harmonised guideline integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2) Current Step 2 version dated 11 June 2015.

11 SIGNATURE PAGE(S)

Protocol Title: A Phase 2, Prospective, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Saroglitazar Magnesium 2 mg and 4 mg in Patients with Non-alcoholic Steatohepatitis.

RESPONSIBILITY	NAME AND DESIGNATION	DATE AND SIGNATURE
PROTOCOL AUTHOR	[redacted]	[redacted]
QUALITY ASSURANCE	[redacted]	[redacted]
MANAGEMENT APPROVAL	Deven V Parmar, MD FCP [redacted]	[redacted]

SPONSOR APPROVAL

STUDY TITLE: A Phase 2, Prospective, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Saroglitazar Magnesium 2 mg and 4 mg in Patients with Non-alcoholic Steatohepatitis.

I have read, understood and approve this protocol.

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

[redacted] Date: 02/08/2018

AUTHORIZED SIGNATORY

Deven V Parmar, MD FCP

[redacted]

DECLARATION OF PRINCIPAL INVESTIGATOR

STUDY TITLE: A Phase 2, Prospective, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Saroglitazar Magnesium 2 mg and 4 mg in Patients with Non-alcoholic Steatohepatitis.

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

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

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

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

[redacted]

Signature

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

[redacted]

12 APPENDICES

Appendix 1: List of Known CYP2C8 Inhibitors/Substrates

Selected inducers, inhibitors and substrates of CYP2C8		
Substrates	**Inhibitors**	**Inducers**
a. Amodiaquine[a] (antimalarial, anti-inflammatory) b. Cerivastatin[a] (statin) c. Enzalutamide (antiandrogen) d. Paclitaxel[a](chemotherapeutic) e. Repaglinide[a] (antidiabetic) f. Torsemide[a] (loop diuretic) g. Sorafenib[a] (tyrosine kinase inhibitor) h. Rosiglitazone (antidiabetic) - converted to active metabolites[b] i. Buprenorphine (semisynthetic opioid) j. Polyunsaturated fatty acids k. Montelukast (leukotriene receptor antagonist)	**Strong** a. Gemfibrozil[a](Hypolipidemic) **Moderate** a. Trimethoprim[a](Antibiotic) **Unspecified potency** a. Thiazolidinediones[a](antidiabetic) b. Montelukast[a](leukotriene receptor antagonist) c. Quercetin[a](antiinflammatory)	**Unspecified potency** a. Rifampicin[a](Antibiotic)
[a] Flockhart DA (2007). "Drug Interactions: Cytochrome P450 Drug Interaction Table". Indiana University School of Medicine. Retrieved on July 2011 [b] Chapter 26 in: Rod Flower; Humphrey P. Rang; Maureen M. Dale; Ritter, James M. (2007). Rang & Dale's pharmacology. Edinburgh: Churchill Livingstone. ISBN 0-443-06911-5		

Appendix 2: NAFLD Activity Score

NAFLD Activity Score		
Item	**Definition**	**Score/Code**
Low- to medium-power evaluation of parenchymal involvement by steatosis		
Steatosis	**<5%**	0
	5% -33%	1
	>33% -66%	2
	>66%	3
Inflammation		
Lobular Inflammation	**No foci**	0
	<2 foci per 200 X field	1
	2-4 foci per 200 X field	2
	>4 foci per 200 X field	3
Liver cell injury		
Ballooning*	**None**	0
	Few balloon cells	1
	Many cells/prominent ballooning	2
*Ballooning classification: few indicates rare but definite ballooned hepatocytes as well as case that are diagnostically borderline		
Final NAFLD Activity Score = Steatosis Score + Lobular Inflammation Score + Ballooning Score		
Fibrosis Score		
Item	**Definition**	**Score/Code**
Fibrosis Stage	**None**	0
	Perisinusoidal or periportal	1
	Mild, zone 3,perisinusoidal	1A
	Moderate, zone3, perisinusoidal	1B
	Portal/periportal	1C
	Perisinusoidal and portal/periportal	2
	Bridging fibrosis	3
	Cirrhosis	4
Adapted from: Design and Validation of a Histological Scoring System for Non-alcoholic Fatty Liver Disease. (HEPATOLOGY, Vol. 41, No. 6, 2005 KLEINER ETAL.)		

APPENDIX 3: Normal Laboratory Range