Protocol No.	SARO.17.009
Version No. and dated	5.0, dated 06 February 2020
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Investigational Product(s)	Saroglitazar Magnesium 4 mg Tablets
IND Number	IND 138351
Study/Scientific Title	A Phase 2A, Double-blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Saroglitazar Magnesium 4 mg Tablets for Treating Non-alcoholic Fatty Liver Disease (NAFLD) in Women With Polycystic Ovary Syndrome (PCOS).
Public Title	Saroglitazar Magnesium 4 mg for the treatment of NAFLD in Women With PCOS.
Clinical Phase	Phase 2A
Sponsor	Zydus Discovery DMCC [redacted]
Study Director (Sponsors Representative)	Dr Deven V Parmar MD, FCP Senior Director & Head – Clinical R & D [redacted]
Sponsors Medical Experts	Dr. Deven V Parmar, MD, FCP Senior Director & Head – Clinical R & D [redacted]
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Confidentiality Statement	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.

STUDY PROTOCOL SUMMARY

Name of Sponsor	Zydus Discovery DMCC [redacted]
Name of the Test Product	Saroglitazar Magnesium 4 mg Tablets
Name of Active Ingredient of Test Product	Saroglitazar Magnesium 4 mg
Name of the Reference Drug	Placebo Tablet
Name of Active Ingredient of Reference Product	Placebo
Study Population	Non-alcoholic Fatty Liver Disease (NAFLD) in women with Polycystic Ovary Syndrome (PCOS)
Study Subjects	Patients of PCOS with NAFLD
Number of Subjects	90
Planned Study Period	34 weeks

Study Title: A Phase 2A, Double-blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Saroglitazar Magnesium 4 mg Tablets for Treating NAFLD in Women With PCOS.

Background: Polycystic ovarian syndrome is the most common endocrine disorder of women of reproductive age, affecting 9-18% of women aged 27-34 years. Polycystic ovarian syndrome is diagnosed when women present with two of the three following features: (a) ovarian dysfunction or anovulation (commonly oligomenorrhea), (b) hyperandrogenemia and (c) polycystic ovaries after excluding hyperprolactinemia, thyroid disease or congenital adrenal hyperplasia.

Polycystic ovarian syndrome can present as one of the four phenotypes based on the number and pattern of criteria that are fulfilled; phenotype 1 where all three criteria are met, phenotype 2 where patients have anovulation and hyperandrogenism, phenotype 3 where patients have polycystic ovaries and hyperandrogenism and phenotype 4 where patients have anovulation and polycystic ovaries. There are a number of important knowledge gaps in the field of PCOS and NAFLD. These can be broadly categorized into (a) there is high prevalence of NAFLD and perhaps Non-alcoholic steatohepatitis (NASH); (b) there is higher likelihood of advanced fibrosis prematurely and at an earlier age; (c) mechanistic basis for prevalence and severity of NAFLD; and (d) novel treatments.

Effective therapies for NAFLD/NASH in this population are missing. The Dual Peroxisome Proliferator-Activated Receptor Alpha/Gamma (PPAR- α/γ) agonist, Saroglitazar Magnesium, has demonstrated lipid and glucose lowering effects through its PPAR α and γ activation. It is already approved for treatment of dyslipidemia in patients with diabetes in some countries and to date exhibited excellent tolerability and safety. It also reduces fasting blood glucose and hemoglobin A1c in these patients. Being predominantly a PPAR α agonist, with weaker γ stimulating effects, it has the advantage of inducing fewer side effects than previously identified with PPAR γ activation, such

as weight gain and peripheral edema.

Saroglitazar Magnesium improved hepatic steatosis, inflammation and fibrosis in rodent models of NAFLD and NASH. Saroglitazar Magnesium resulted improvement in the lipoproteins and triglyceride levels as well as measures of insulin sensitivity.

In this phase 2A pilot trial, we will test the efficacy and safety of Saroglitazar Magnesium on NAFLD patients with PCOS. If efficacy and safety are shown, that will provide a strong basis for long term evaluation of decreasing the disease burden for patients with PCOS and NAFLD.

Objectives:

Objective:
The purpose of this study is to evaluate the efficacy and safety of Saroglitazar Magnesium 4 mg Tablets once-daily in women with well characterized PCOS diagnosed with NAFLD.

Primary Objective:

To evaluate the effect on hepatic fat content, measured as proton-density fat-fraction (PDFF) by magnetic resonance imaging (MRI), of once-daily Saroglitazar Magnesium 4 mg Tablets for 24 weeks vs placebo.

Secondary Objectives:

To assess the effect of a 24-week treatment regimen of once-daily Saroglitazar Magnesium 4 mg Tablets on the following parameters in patients of PCOS with NAFLD:

1. Liver enzymes/LFTs.
2. Insulin resistance (IR) measured by Homeostasis Model Assessment (HOMA).
3. Liver stiffness measurement obtained via transient elastography/FibroScan®.
4. Controlled attenuation parameter obtained via transient elastography/ FibroScan®.
5. Body weight, body mass index (BMI) and waist circumference.
6. MRI-derived total liver fat index and total liver volume.
7. Serum lipid profile and lipoproteins.
8. Sex hormone binding globulin.
9. Ovarian function.
10. Free androgen index.
11. Pharmacokinetics of Saroglitazar following first dose and last dose.

Criteria for Safety:

1. Vitals: blood pressure (BP) (sitting BP after 05 min rest; systolic and diastolic BP), pulse rate, oral temperature and respiratory rate (at Visit 1 [Screening] and at Visit 3 through Visit 8 [End-of-Treatment]).

2. Body mass index (BMI) at Screening Visit (Visit 1), at 12 weeks (Visit 6) and at the Week 24 End-of-Treatment visit (Visit 8).

3. Waist measurements at Screening Visit, at Visit 6 and at the End-of-Treatment visit.

4. The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, pelvic, breast, chest, heart, lungs, abdomen, skin, extremities, neurological systems, musculoskeletal systems and weight measurement. Investigator should also evaluate the patients for hirsutism and virilizing signs (upper lip, chin, chest, upper abdomen, lower abdomen, thighs, back, arm and buttocks). Note: Breast examination will be done as part of screening. Pelvic examination will be performed as part of screening, if not performed within 6 months of randomization.

5. Laboratory assessment

    a. Hematology: Hematocrit, hemoglobin, mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, mean platelet volume, red blood cell (RBC) count, white blood cell (WBC) count, differential WBC count.

    b. Liver enzymes/liver function tests (LFTs): aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (with conjugated bilirubin), gamma glutamyltransferase (GGT), serum protein and albumin.

    c. Renal function tests (RFTs): blood urea nitrogen (BUN), creatinine and estimated glomerular filtration rate (eGFR). Estimated glomerular filtration rate will be calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

    d. Inflammatory marker: high sensitivity C-reactive protein (hs-CRP).

    e. Lipid profile and lipoproteins: triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), small dense low-density lipoprotein (sdLDL), very low density lipoprotein (VLDL), free fatty acids, apolipoprotein A and apolipoprotein B.

    f. Urine examination: physical examination (appearance, color, specific gravity and pH); microscopy (epithelial cells, red blood cells, pus cells, cast and crystals) and chemical examination (protein, glucose, bilirubin, urobilinogen, ketone bodies and nitrite).

    g. T3, T4 and thyroid stimulating hormone (TSH)

    h. Serum pregnancy test

    i. Urine pregnancy test

    j. Serology: human immunodeficiency virus (HIV) type 1 and type 2, hepatitis A virus (HAV), anti-hepatitis B virus surface antigen (HBsAg) and hepatitis C virus (HCV) (at Visit 1).

    k. International normalized ratio (INR) and prothrombin time (PT)

    l. Cytokeratin 18

    m. Free androgen index and Sex hormone binding globulin level

n. Total testosterone and free testosterone

o. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels

p. 17-hydroxyprogesterone

q. Estradiol

r. Creatine Kinase (CK)

s. Cardiac function: 12-lead-electrocardiogram (ECG)

t. Glycemic control: Fasting plasma glucose (FPG), HbA1c and plasma insulin levels

u. B-type natriuretic peptide (BNP) and aminoterminal fragment of BNP prohormone (NT-proBNP)

v. Papanicolaou (PAP) test

w. Cardiac troponin, creatine kinase-muscle/brain (CK-MB)

x. Lipase and amylase

y. Uric acid

6. Adverse event(s): Frequency and severity of adverse event (AE) /serious adverse events (SAEs), drop-outs due to AEs/SAEs for all subjects enrolled will be recorded. All AEs, will be assessed using Council for International Organizations of Medical Sciences (CIOMS) criteria using:
   a. Causality
   b. Severity
   c. Seriousness
   d. Expectedness

Note: Efficacy assessments and laboratory assessments (liver fat content by MRI-PDFF [MRI-PDFF will be performed during screening phase, screening phase results will be used as the baseline assessment], controlled attenuation parameter, hormonal profile, fasting plasma glucose, lipid and lipoprotein profiles, MRI-derived total liver fat index and total liver volume [MRI-derived total liver fat index and total liver volume assessment will be performed during screening phase, screening phase results will be used as the baseline assessment], plasma insulin levels, homeostasis model assessment (insulin resistance [HOMA-IR]), liver stiffness by transient elastography/FibroScan®, ovarian function, liver enzymes/LFTs, hematology, coagulation test (PT/INR), renal function test, CK, hs-CRP, BNP, NT-proBNP, cardiac troponin, CK-MB, lipase and amylase, TNFα, uric acid, TSH, T3 and T4, serology, HIV type 1 and type 2, HAV, anti-HBsAg, HCV, serum pregnancy test, urine microscopy and urine chemistry) which will be done at Visit 1 will be considered for baseline visit. PAP test, endometrial biopsy and mammography will be performed as per Time and Events Schedule.

Criteria for Inclusion/Exclusion

Inclusion criteria:

1. Females, 18 to 45 years of age.
2. Previously confirmed diagnosis of PCOS by Rotterdam criteria (at least 2 of 3):
   1) oligo-and/or anovulation;
   2) hyperandrogenism (clinical and/or biochemical) ;
   3) polycystic ovary morphology on ultrasonography (either 12 or more follicles measuring 2–9 mm in diameter or an increased ovarian volume >10 cm^3).
3. Evidence of NAFLD within 6 months prior to the Screening Visit (Visit 1). The diagnosis of NAFLD is made according to the American Association for the Study of Liver Diseases (AASLD) criteria.

   a) hepatic steatosis by imaging or histology,

   b) no significant alcohol consumption,

   c) no competing etiologies for hepatic steatosis, and

   d) no co-existing causes for chronic liver disease.

4. Alanine transaminase ≥ 38 U/L at Visit 1. Visit 2 ALT must not increase >30% from Visit 1.
5. Hepatic fat fraction ≥10% by MRI-PDFF.
6. Willingness to participate in the study.
7. Ability to understand and give informed consent for participation.
8. A normal pelvic examination within past 6 months before randomization.
9. A normal breast examination at screening (If Mammogram has been done in the preceding 12 months it will be documented. If patient is not up to date with standard breast cancer screening guidelines and is willing to receive screening, mammogram will be offered prior to enrollment as part of standard care).
10. A normal Papanicolaou (PAP) test within past 6 months before randomization (If PAP test has not been performed within 6 months of the screening visit, it must be performed during screening).
11. Woman who agrees to use the following contraceptive methods:
    a. Combination hormonal contraceptives (including pills, patches and vaginal rings).

    For the following conditions, the usage of the combination hormonal contraceptives should be based upon a discussion with the subject and the investigators' clinical judgment.

    i. Women greater than 35 years of age who also smoke fewer than 15 cigarettes per day
    ii. Adequately controlled hypertension
    iii. Properly taken blood pressure above a systolic 140-159 mm Hg or diastolic 90- 99 mm Hg

iv. Known hyperlipidemia
v. Diabetes associated with vascular disease, including neuropathy, retinopathy and nephropathy.
vi. Diabetes duration greater than 20 years.

b. Women with the following conditions should use effective methods other than combined hormonal contraceptives (for e.g., Progestogen-only oral contraceptives or progestogen-containing intrauterine devices (IUD), Non-hormonal IUD, Double-barrier contraception [e.g., condom plus diaphragm]):
   i. Women greater than 35 years of age who also smoke 15 or more cigarettes per day
   ii. Properly taken blood pressure above systolic ≥ 160 mm Hg or diastolic ≥ 100 mm Hg
   iii. Known hyperlipidemia
   iv. Vascular disease, including neuropathy, retinopathy and nephropathy
   v. Diabetes duration greater than 20 years.

Exclusion criteria:

1. Presence of other chronic liver diseases (hepatitis B or C, autoimmune hepatitis, cholestatic liver disease, Wilsons disease, hemochromatosis, etc.).
2. Average alcohol consumption ≥ 7 drinks per week for women in the 6 months prior to enrollment. Subjects will be required to have an "Alcohol Use Disorder Identification Test" (AUDIT) score of <8.
3. Clinical, imaging, or histological evidence of cirrhosis
4. Any of the following laboratory values:
   a. Hemoglobin <10 g/dL
   b. White blood cell count <4 x 10^9/L
   c. Neutrophil count <1.5 × 10^3/µL
   d. Abnormal baseline platelet counts (<150 x 10^3 uL).
   e. Total serum bilirubin greater than the ULN (>1.3 mg/dL) (except in patient with known Gilbert Syndrome where TB up to 2.5 mg/dL is allowed)
   f. Albumin <3.2 g/dL
   g. Serum ALT or AST >250 IU/L
   h. Lipase or amylase more than the ULN at baseline.
   i. Serum creatinine ≥1.5 mg/dL
   j. Renal impairment as demonstrated by baseline estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated using the CKD-EPI equation).
   k. Total creatine kinase level more than the ULN at baseline.
5. Patient with INR >1.3
6. Patients who have used medications known to cause hepatic steatosis (e.g., corticosteroids, amiodarone, methotrexate, tetracycline, tamoxifen, anabolic steroids, or valproic acid) for more than 2 weeks in the past year.
7. Prior bariatric surgery.
8. Weight loss of more than 5% in the 3 months preceding screening.
9. Severe co-morbidities (e.g., advanced cardiac, renal, pulmonary, or psychiatric illness).

10. Known allergy, sensitivity or intolerance to Saroglitazar Magnesium, comparator or formulation ingredients (Saroglitazar Magnesium Micronized, Magnesium Oxide Light, Microcrystalline Cellulose, Anhydrous Lactose, Croscarmellose Sodium, Povidone k 30, Talc (luzena c), Colloidal Silicon Dioxide and Magnesium Stearate).
11. Use of antidiabetic and lipid lowering medications if the dose is not stable for at least the 3 months preceding screening.
12. Intake of Vitamin E (>100 IU/day) or multivitamins containing Vitamin E (>100 IU/day) 3 months before enrollment.
13. Use of drugs with potential effect on NAFLD/NASH such as S-adenosylmethionine (SAM-e), Betaine, Pentoxifylline, Thiazolidinediones (Pioglitazone, Rosiglitazone), Obeticholic Acid or Milk Thistle in the 3 months prior to screening.
14. Changing doses of statins (Simvastatin, Pravastatin, Atorvastatin, Fluvastatin, Lovastatin, Rosuvastatin) or Fibrates (Clofibrate, Fenofibrate) in the 3 months prior to enrollment.
15. Illicit substance abuse within the past 12 months.
16. Pregnant or breast-feeding females.
17. Poorly controlled diabetes with HbA1c >8.5%.
18. Use of total parenteral nutrition in the 6 months preceding enrollment.
19. Women with known Cushing syndrome or hyperprolactinemia.
20. Late onset congenital adrenal hyperplasia, androgen-producing tumors.
21. Refusal or inability to comply with the requirements of the protocol, for any reason, including scheduled clinic visits and laboratory tests.
22. History of myopathies or evidence of active muscle diseases.
23. History or current significant cardiovascular disease, including:
    i. Unstable angina (i.e., new or worsening symptoms of coronary heart disease within the past 3 months before screening), acute coronary syndrome within the past 6 months before screening, acute myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months before screening.
    ii. History or current unstable cardiac dysrhythmias within prior 3 months before screening.
    iii. Uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg).
    iv. Stroke or transient ischemic attack prior 6 months before screening visit.
24. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer.
25. History of bladder disease other than urinary tract infection or cystitis. Previous or current hematuria due to etiologies other than urinary tract infection or kidney stones.

Methodology:

- This is a multicenter, phase 2A, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Saroglitazar Magnesium in women with well characterized PCOS, 18-45 years of age diagnosed with NAFLD according to the AASLD criteria within 6 months preceding the Screening Visit (Visit 1). Six patients in each group are planned for pharmacokinetic assessment therefore a total of 12 patients will be included. Additional patients may be enrolled into the study to ensure the pharmacokinetic assessment is performed on at least 6 completed patients in each treatment arm.

- Eligible subjects will be screened within 4 weeks prior to randomization. During the Visit 1, subject will be seen by the investigator or designated study personnel and an AUDIT questionnaire will be administered. Inclusion and exclusion criteria will be verified during Visit 1 and Visit 3.
- Eligible subjects will be enrolled into either of the two treatments arms: Saroglitazar Magnesium 4 mg Tablets and matching placebo tablets in a 1:1 ratio.
- The study will be conducted over a period of up to 34 weeks. Subjects will be evaluated at study sites for 8 scheduled visits: at screening visits (Visit 1: Day [-28], Visit 2: Day [-14 to -7]), randomization (Visit 3: Week 1, Day 1), Visit 4 (Week 2, Day 14), Visit 5 (Week 8, Day 56), Visit 6 (Week 12, Day 84), Visit 7 (Week 16, Day 112) Visit 8 (Week 24, Day 168). After completion of the study treatment period, the subjects will be followed for an additional period of 6 weeks without study medication until Visit 9 (Week 30, Day 210).
- Subjects will be monitored during the study and in every visit for development of any adverse events including drug induced liver injury. In addition to physical examination, laboratory data and ECGs done during the study period will be monitored to detect any treatment emergent adverse events. The schedule of assessments is presented in Table 1 (Time and Events Schedule).

Pre-screening Visit: An informed consent will be obtained from the potential subjects before any pre-screening evaluations. The study sites may identify potential subjects by conducting a laboratory evaluation of the ALT levels. This optional pre-screening can be conducted before the actual study screening. A subject with an ALT ≥38 U/L may be considered for the actual study screening. Also, along with the evaluation of the ALT levels, in those potential subjects who do not have a documented diagnosis of NAFLD through any imaging method, an optional abdominal ultrasound or Fibroscan® may be performed during the pre-screening.

In addition, an optional lab evaluation for diagnosis of PCOS through lab or ultrasound may be performed during pre-screening. The evaluation of the ALT levels during the pre-screening will be done at the local laboratory, whereas the laboratory evaluations during the screening and the treatment phase will be done at the central laboratory.

Screening Phase

Visit 1 (Day -28): In this study, the screening phase will consist of 28 days. Unless otherwise specified, screening procedures may be completed at any time during the screening period. Before each patient is enrolled to the study, informed consent will be obtained from the patient (or her legally authorized representative) according to the regulatory and legal requirements of the participating country. Patient eligibility for participation in the study will be assessed. Current social, medical and ovarian dysfunction history will be obtained and physical examination, vital signs, ECGs, laboratory evaluations (including serology, hematology, lipid and lipoprotein profiles, liver enzymes/LFTs, BNP, NT-proBNP, cardiac troponin, CK-MB, lipase and amylase, hormonal profile and urinalysis) will be performed. PAP test, endometrial biopsy and mammography will be performed as per Time and Events Schedule. Patients will undergo a serum pregnancy test.

Visit 2 (Day -14 to -7): Liver function tests (AST, ALT, ALP, GGT, total-protein, albumin, total bilirubin (with conjugated bilirubin) will be re-measured approximately 2 weeks from Day -28 to determine eligibility.

Alanine transaminase ≥ 38 U/L at Visit 1. Visit 2 ALT must not increase >30% from Visit 1.

Randomization and Treatment Phase

- The randomization and treatment phase will include 6 outpatient visits (Visit 3 to Visit 8) over a period of 24 weeks including the randomization visit.
- All the eligible subjects will be randomly assigned into either of the two treatments arms: Saroglitazar Magnesium 4 mg Tablets and matching placebo tablets in a 1:1 ratio.
- Efficacy assessments will be conducted at 12 (hormonal profile, lipid and lipoprotein profiles, ovarian function and liver enzymes/LFTs) and 24 weeks (liver fat content by MRI-PDFF, hormonal profile, lipid and lipoprotein profiles, MRI-derived total liver fat index and total liver volume, homeostasis model assessment [insulin resistance (HOMA-IR)], liver stiffness by transient elastography/FibroScan®, controlled attenuation parameter, ovarian function and liver enzymes/LFTs).
- In addition, subjects will be monitored during the study and at every visit for development of any adverse events including drug induced liver injury.
- In addition to physical examination, laboratory data and ECGs done during the study period will be monitored to detect any treatment emergent adverse events. Detailed efficacy and safety assessments are provided in Table 1 (Time and Events Schedule).

End-of-treatment Visit (Visit 8): An end-of-treatment visit will occur at 24 weeks for clinical assessment, reconciliation of study drug, and measurements of efficacy and safety endpoints. Detailed efficacy and safety assessments are provided in Table 1 (Time and Events Schedule).

Safety follow-up visit (Visit 9): A final post-treatment visit will occur 6 weeks (±3 days) after the end-of-treatment visit for safety monitoring. A telephonic follow-up visit will be performed to assess any AE or SAE after the end-of-treatment visit for safety monitoring.

Patient Withdrawal:
Patients may withdraw from the entire study at any time without penalty and for any reason without prejudice to her future medical care. A patient's withdrawal of consent and agreement to undergo a final examination will be documented on the electronic case report form. As far as possible, all assessments scheduled for end-of-treatment must be performed on all patients who receive the study drug but do not complete the study according to protocol.

Discontinuation of Patients from the Study or Study Drug:

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

- Noncompliance to the protocol requirements.
- Occurrence of a serious or intolerable AE and based upon the Investigators' clinical

judgment.

- The Sponsor or PI terminates the study.
- Either the PI or the Sponsor decides that discontinuing the study or discontinuing the patient is in the patient's best interest.
- For reasons related to safety.
- The patient is lost to follow-up.
- A patient may also be discontinued from study drug/study by the Sponsor, Regulatory Authorities or Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
- If the patient becomes pregnant.

Concomitant medications:
All the permitted and excluded concomitant medications will be recorded in this study**.**

Total Enrollment:	Ninety patients are planned to be enrolled in this study. Patients will be randomly assigned to receive active drug (Saroglitazar Magnesium 4 mg) or placebo in a 1:1 ratio. Six patients in each group are planned for pharmacokinetic assessment therefore a total of 12 patients will be included.
Test Product: **Dose:** **Mode of Administration:**	Saroglitazar Magnesium tablet (Zydus) 4 mg Oral (once daily in the morning before breakfast without food)
Reference/Placebo Therapy: **Mode of Administration:**	Placebo tablet Oral (once daily in the morning before breakfast without food)
Duration of Treatment:	24 weeks

Criteria for Efficacy

Primary Efficacy Endpoint:

Change in hepatic fat content from baseline following 24 weeks of treatment as measured by MRI-PDFF.

Secondary Efficacy Endpoints:

1. Changes from baseline to Week 12 and Week 24 in liver enzymes/LFTs: ALT, AST, ALP, GGT, serum protein, albumin and total bilirubin.
2. Changes from baseline to Week 12 and Week 24 in IR as measured by HOMA.
3. Changes from baseline to Week 24 in markers of liver injury and fibrosis including CK-18, high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor α (TNFα), and liver stiffness measured by transient elastography/FibroScan®.
4. Changes from baseline to Week 24 in controlled attenuation parameter measured by transient elastography/FibroScan®.
5. Changes from baseline to Week 12 and Week 24 in body weight, BMI and waist circumference.
6. Changes from baseline to Week 24 in MRI-derived measures of total liver fat index and total liver volume.
7. Changes from baseline to Week 12 and Week 24 in lipid and lipoprotein levels: TG, TC,

HDL, LDL, sdLDL, VLDL, apolipoprotein A and apolipoprotein B.
8. Changes from baseline to Week 12 and Week 24 in sex hormone binding globulin (SHBG) level.
9. Changes from baseline to Week 12 and Week 24 in ovarian function (Total testosterone, 17-hydroxyprogesterone, free testosterone, luteinizing hormone, follicle-stimulating hormone, LH-to-FSH ratio and estradiol).
10. Changes from baseline to Week 12 and Week 24 in free androgen index.
11. Pharmacokinetics of Saroglitazar following first dose and last dose.

Criteria for Safety

1. Frequency and severity of AEs and serious AEs.
2. Clinical laboratory testing (hematology, clinical chemistry, hormonal profile and urinalysis).
3. Twelve-lead electrocardiogram.
4. Vital signs.
5. Physical examination.

Statistical Methods:

General data analysis: Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock. The SAP will include detailed statistical aspects of the efficacy and safety analysis. Statistical analysis will be performed using SAS® software (version 9.4 or higher) (SAS Institute Inc., USA).

Demographic and baseline characteristics will be summarized by treatment and population set. Subject disposition and reason for withdrawal will be summarized and presented.

Unless otherwise stated, all the continuous variables will be summarized using descriptive statistics such as n, mean, standard deviation, minimum, median and maximum. Categorical variables will be summarized using frequencies and percentages.

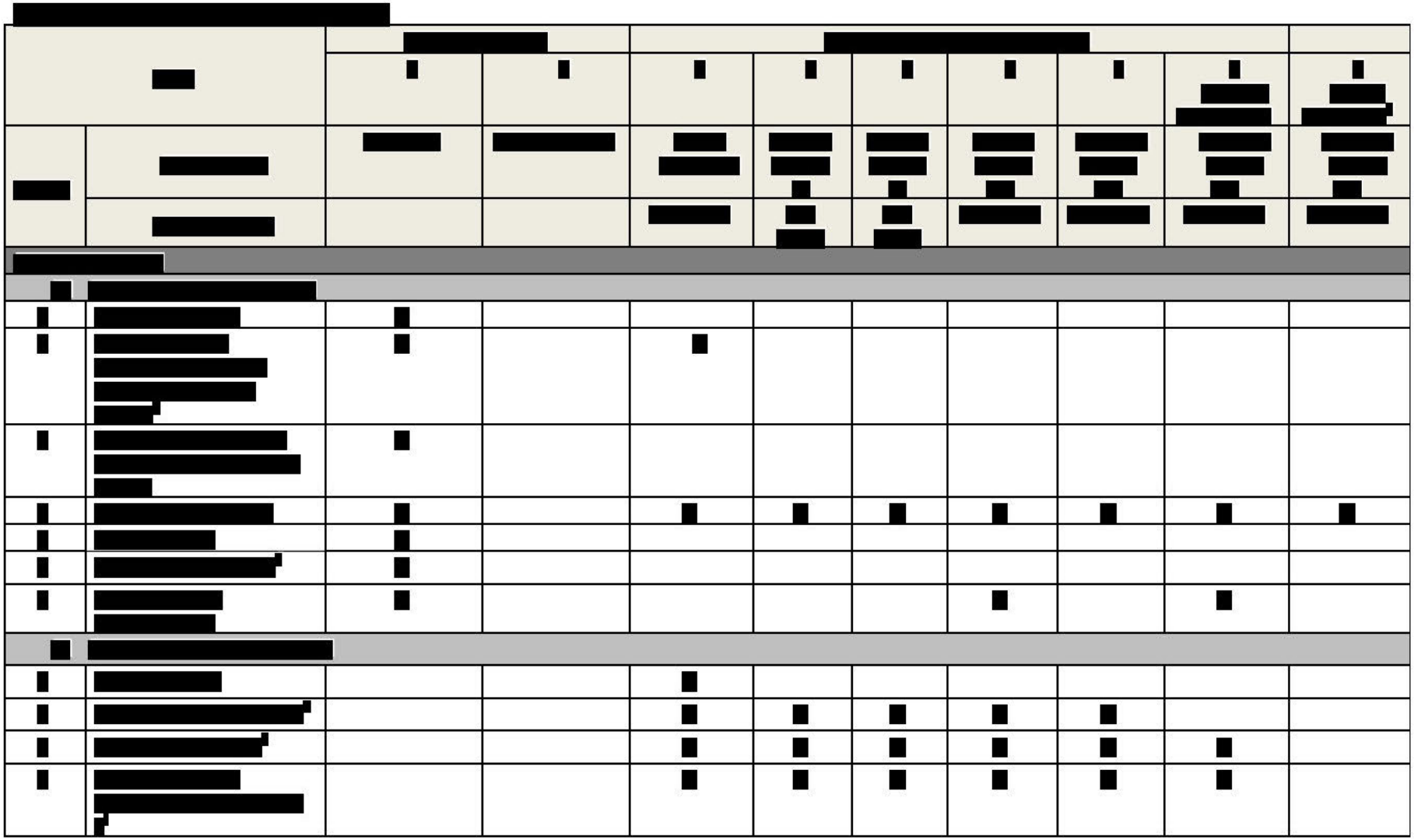
Efficacy analysis: All efficacy analysis will be based primarily on the Per Protocol (PP) population and analysis based on modified intent-to-treat (mITT) population will be considered as supporting analyses for this proof of concept study. The PP population is a subset of mITT population. The PP population will consist of all randomized patients completing the treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome (i.e., had both baseline and end-of-treatment MRI & has taken ≥80% and ≤120% of the study drug).The mITT population will consist of all randomized patients who received at least one dose of the study drug 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.

Primary efficacy analysis: The primary analysis for primary efficacy endpoint will be based on PP population. The primary efficacy endpoint in this study is the change in hepatic fat content from baseline following 24 weeks of treatment as measured by MRI-PDFF. The change from baseline of hepatic fat will be determined as (Week 24 value – Baseline value). The change from baseline at Week 24 in hepatic fat content between treatments will be evaluated using analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline value as covariate. Treatment effects will be estimated using the least square means, standard error and 95% confidence interval (CI) from the ANCOVA model. The two treatment groups, i.e., Saroglitazar Magnesium 4 mg Tablets versus Placebo, will be compared using difference in least-square means and p-values from the ANCOVA model.

Secondary efficacy analysis: All secondary efficacy endpoints will be analyzed using the same statistical methods as primary efficacy endpoint.

Descriptive statistics will be provided for all pharmacokinetic parameters.

Safety analysis: Safety analysis will be based on the safety population which will consist of all randomized patients who received at least 1 dose of study drug. All patients in the safety population will be analysed according to the actual treatment received. All safety endpoints (AEs, clinical laboratory testing, ECGs, body weight, physical examination and vital signs) will be summarized by treatment group using the following descriptive statistics: N, mean, median, standard deviation, minimum and maximum for continuous variables, frequencies and percentages for categorical variables.



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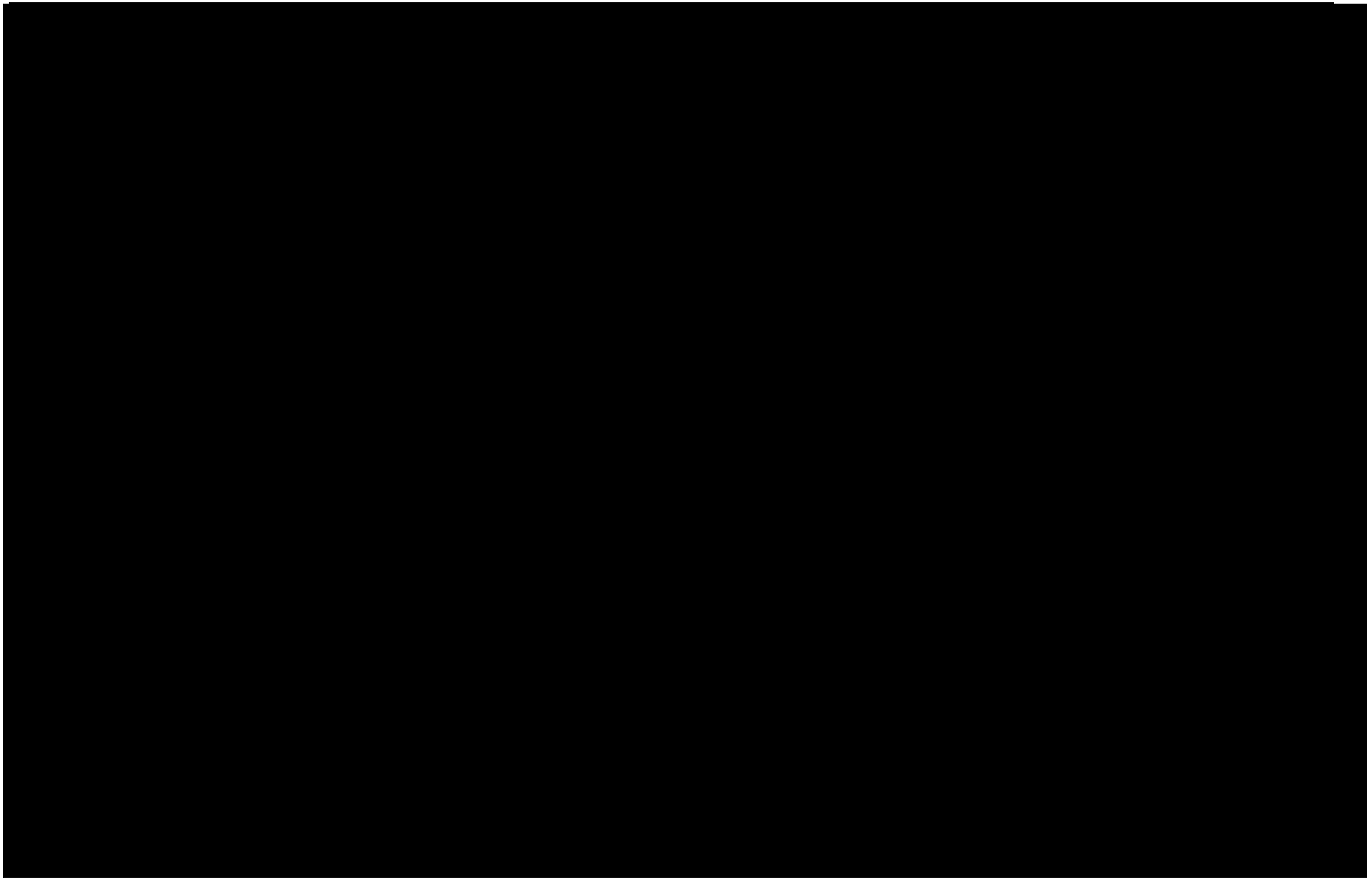

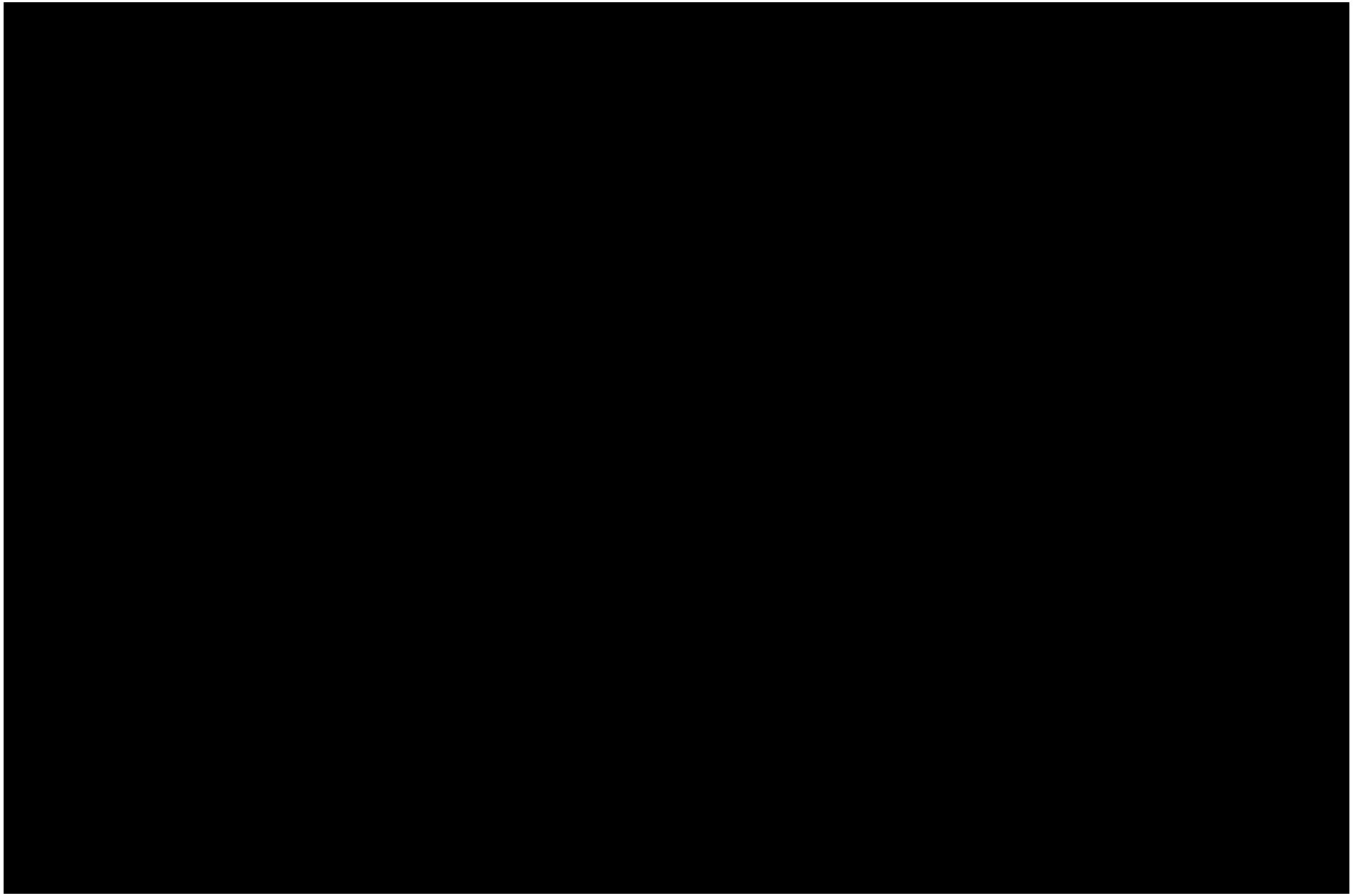

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ABBREVIATIONS

Abbreviation	Definition
AEs	Adverse events
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AASLD	American Association for the Study of Liver Diseases
AST	Aspartate aminotransferase
ANCOVA	Analysis of covariance
AUDIT	Alcohol Use Disorder Identification Test
BP	Blood pressure
BMI	Body mass index
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CIOMS	Council for International Organization of Medical Sciences
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Event
CRA	clinical research associate
CK	Creatine Kinase
CK-MB	Creatine kinase-muscle/brain
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FA	Fatty acids
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HAV	Hepatitis A virus
HbA1c	Glycated hemoglobin
HCV	Hepatitis C virus

HBsAg	Hepatitis B virus surface antigen
HDL	High density lipoprotein
HOMA	Homeostasis Model Assessment
HIV	Human immunodeficiency virus
hs-CRP	High sensitivity C-reactive protein
INR	International Normalized ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IR	Insulin resistance
IRB	Institutional Review Board
LDL	Low density lipoprotein
LFT	Liver function test
LPL	Lipoprotein lipase
LH	luteinizing hormone
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PAP	Papanicolaou
PT	Prothrombin time
PI	Principal Investigator
PCOS	Polycystic ovarian syndrome
PDFF	Proton-density fat-fraction
MPV	Mean platelet volume
PPAR	Peroxisome proliferator-activated receptor
PP	Per protocol
QD	Quarter-in-die
RBC	Red blood cell
RFT	Renal function test
SAE	Serious adverse event

SAM-e	S adenosylmethionine
sdLDL	small dense low-density lipoprotein
SHBG	Sex hormone binding globulin
SAP	Statistical analysis plan
SOPs	Standard operating procedures
TC	Total Cholesterol
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TSH	Thyroid stimulating hormone
TZD	Thiazolidinediones
VLDL	Very low density lipoprotein
WBC	White blood cell

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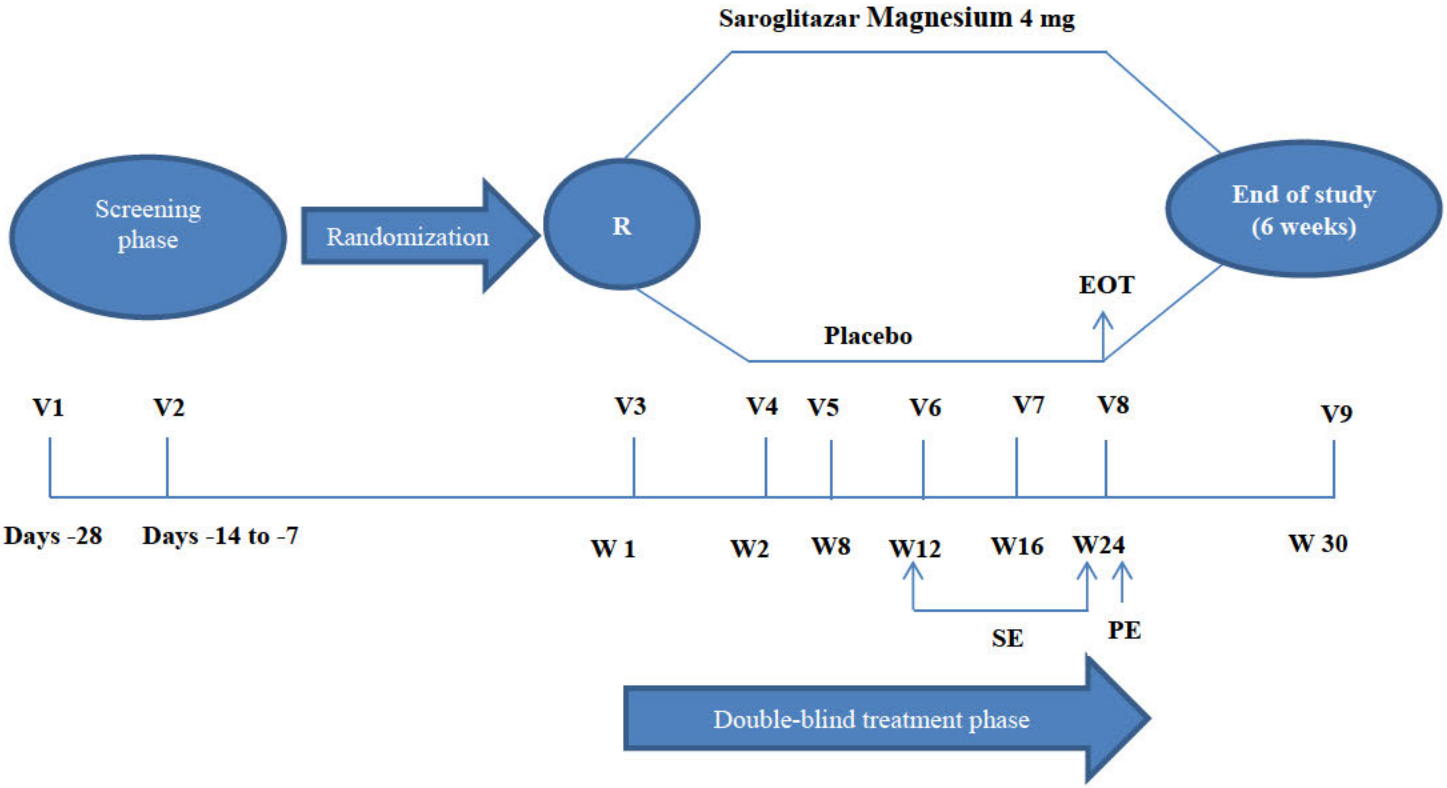
1 STUDY FLOW CHART



Abbreviation: EOT-end-of-treatment, PE-primary endpoint, R-randomization, SE-secondary endpoint, V-visit, W-week

2 INTRODUCTION

2.1 BACKGROUND

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of women of reproductive age, affecting 9-18% of women aged 27-34 years.[1,2] Polycystic ovarian syndrome is diagnosed when women present with two of the three following features: (a) ovarian dysfunction or anovulation (commonly oligomenorrhea), (b) hyperandrogenemia and (c) polycystic ovaries after excluding hyperprolactinemia, thyroid disease or congenital adrenal hyperplasia.[3]

Polycystic ovarian syndrome can present as one of the four phenotypes based on the number and pattern of criteria that are fulfilled; phenotype 1 where all three criteria are met, phenotype 2 where patients have anovulation and hyperandrogenism, phenotype 3 where patients have polycystic ovaries and hyperandrogenism and phenotype 4 where patients have anovulation and polycystic ovaries. Polycystic ovarian syndrome phenotype 1 has been shown to be more commonly associated with insulin resistance (IR) compared to the rest.[4] Insulin resistance state is also believed to contribute to hyperandrogenism; excess insulin in such states increases sensitivity of pituitary to gonadotropic hormone releasing hormone thus increasing steroidogenesis in the ovaries; insulin also appears to stimulate 17-α hydroxylase and 3β-hydroxysteroid dehydrogenase, increasing adrenal androgen secretion while inhibiting sex hormone binding globulin. Subjects, males and females with metabolic syndrome (MS) were found to have low sex hormone binding globulin (SHBG).[5]Among patients with PCOS, those with MS also showed low SHBG levels compared to those without metabolic syndrome.[6] But the levels were no longer different after adjusting for body mass index (BMI) and insulin resistance (IR).[6] In a prospective study where patients with PCOS were compared to those without PCOS, we learn that subjects with MS have similar homeostatic model assessment (HOMA)-IR compared to those who do not regardless of PCOS diagnosis. Subjects with PCOS and MS had higher serum androgen levels compared to those without PCOS and metabolic syndrome. Almost two thirds of patients with PCOS have insulin resistance.[7] Up to 67% patients with IR have non-alcoholic fatty liver disease (NAFLD).[8] This suggests that patients with PCOS are at higher risk of NAFLD. In fact, patients with PCOS have been shown to have high prevalence of NAFLD, diagnosed based on imaging and clinical criteria.[9] Some studies suggested that women with PCOS and NAFLD may have more advanced hepatic histology. While there are numerous clinical trials ongoing for non-alcoholic steatohepatitis NASH/NAFLD in the general population there are no studies targeting women with PCOS. Arguably, women with PCOS and NAFLD are an important subgroup of patients needing specific attention because of their risk for advanced fibrosis and potentially different mechanistic basis.

There are a number of important knowledge gaps in the field of PCOS and NAFLD. These can be broadly categorized into (a) prevalence and clinical risk factors for NAFLD in women with well characterized PCOS; (b) spectrum of liver disease severity, characterized non-invasively

and when possible invasively; (c) mechanistic basis for prevalence and severity of NAFLD; and (d) novel treatments.
However, effective therapies for NAFLD/NASH in this population are missing. The Dual Peroxisome Proliferator-Activated Receptor Alpha/Gamma (PPAR- α/γ) agonist, Saroglitazar Magnesium, has demonstrated lipid and glucose lowering effects through its PPAR α and γ activation.[10, 11] It is already approved in India for treatment of hyperlipidemia in patients with diabetes. It also reduces fasting blood glucose and hemoglobin A1c in these patients.[10] Being predominantly a PPAR α agonist, with weaker γ stimulating effects, it has the advantage of inducing fewer side effects than previously identified with PPAR γ activation, such as weight gain and peripheral edema.[12]

2.2 RATIONALE FOR CONDUCTING THE TRIAL

The Dual Peroxisome Proliferator-Activated Receptor Alpha/Gamma agonist, Saroglitazar Magnesium, has demonstrated lipid and glucose lowering effects through its PPAR α and γ activation.[10, 11] It is already approved in India for treatment of hyperlipidemia in patients with diabetes. It also reduces fasting blood glucose and hemoglobin A1c in these patients.[10] Being predominantly a PPAR α agonist, with weaker γ stimulating effects, it has the advantage of inducing fewer side effects than previously identified with PPAR γ activation, such as weight gain and peripheral edema.[12] More recently, an exploratory open label study of Saroglitazar Magnesium was conducted in human immunodeficiency virus (HIV) infected patients with HIV lipo-dystrophy related hypertriglyceridemia.[13] Fifty subjects were on stable antiretroviral therapy (ART) regimen at least for 8 weeks prior enrolling in the 12-week trial. Saroglitazar Magnesium showed improvements in the lipoproteins and triglycerides (TG) levels as well as measures of insulin sensitivity.

Non-alcoholic fatty liver disease is a spectrum of clinical–pathological conditions that can manifest as simple steatosis, characterized by accumulation of lipids in the liver parenchyma, or NASH, characterized by hepatocyte injury, inflammation, and fibrosis. The worldwide prevalence of NAFLD has been estimated to range from 2.8% to 46% depending on the diagnostic method used. The disease is strongly associated with obesity, diabetes mellitus, IR, and MS.[14, 15]

Another element strongly associated with IR and MS is PCOS, which is a common endocrine abnormality in women of reproductive age, and is characterised by chronic anovulation and hyperandrogenism. Insulin resistance is one of the core pathophysiologies of this syndrome, and although the prevalence varies across populations with different backgrounds, obesity is also prevalent (20–70%) in women with PCOS.[16]

The prevalence of NAFLD within the PCOS population is now estimated to be anywhere between 15% and 55%, depending on the diagnostic index used for both NAFLD and PCOS. The pathogenesis of NAFLD is multifactorial, but obesity, MS and IR appear to be pivotal contributing factors. Given that central obesity, MS and IR are shared features in both PCOS and subjects with NAFLD, there is an increasing evidence of higher NAFLD prevalence in women

with PCOS. Since insulin resistance, obesity and MS are common features of both NAFLD and PCOS, We hypothesize that PCOS and NAFLD may coexist. The present study is a phase 2 A, proof-of-concept study, the purpose of the present study is to evaluate the concept of efficacy of Saroglitazar Magnesium 4 mg Tablets once-daily in women with well characterized PCOS diagnosed with NAFLD. Data on safety and tolerability of Saroglitazar Magnesium 4 mg Tablets in PCOS patients diagnosed with NAFLD will also be collected.

2.3 DRUG PROFILE

Saroglitazar, [benzenepropanoic acid, α-ethoxy-4-[2-[2-methyl-5-[4-(methylthio) phenyl]-1H-pyrrol-1-yl]ethoxy]-, magnesium salt (2:1), (αS)], is a novel PPAR agonist with dual PPAR agonistic properties – it is a potent and predominant PPARα agonist with moderate PPARγ agonistic activity.

Peroxisome proliferator-activated receptors are nuclear lipid-activated transcription factors that regulate the expression of various genes involved in the control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. The pharmacological effects of Saroglitazar Magnesium were extensively evaluated in various preclinical models. Saroglitazar Magnesium showed both antidyslipidemic and antidiabetic effects, mainly mediated via activation of PPARα and PPARγ, respectively.

Pre-clinical Experience

Saroglitazar Magnesium is a novel predominately PPARα agonist and moderate PPARγ agonist. Pre-clinical studies with Saroglitazar Magnesium using various animal models wherein, EC50 of PPARα: PPARγ>300; favorably modulated the lipid and glucose profile. Extensive preclinical safety pharmacology, pharmacokinetics and toxicological studies of Saroglitazar Magnesium showed favorable results. It was found to have superior or equivalent safety and efficacy profile compared to marketed fibrates or thiazolidinediones (TZDs) in pre-clinical studies.

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

Although Saroglitazar Magnesium is predominantly a PPARα agonist, it also causes activation of PPARγ and regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilization. Saroglitazar Magnesium increases the expression of numerous PPARγ-responsive genes involved in carbohydrate and lipid metabolism, including

adiponectin, adipocyte fatty-acid-binding protein (aP2), LPL, fatty acid transport protein and fatty acid translocase. By increasing the expression of these genes, Saroglitazar Magnesium decreases the post-prandial rise of plasma free fatty acids, improves postabsorptive insulin-mediated suppression of hepatic glucose output, reduces the metabolic burden on liver and muscle and promotes glucose utilization. Robust antidiabetic and insulin sensitizing effects of Saroglitazar Magnesium were observed in preclinical models, in which hyperglycemia and/or impaired glucose tolerance is a consequence of insulin resistance in target tissues.

Furthermore, two pre-clinical studies were conducted in letrozole induced PCOS animal models. In first study, female Wistar rats of 11-12 weeks were used. Wistar rats develop obesity, hyperglycemia, hyperinsulinemia and PCOS when manipulated using drugs, surgery or by environmental changes. Therefore, this model proves to be suitable for predicting the likely therapeutic benefit of novel treatment for PCOS in humans.

Following observation was recorded after treatment with Saroglitazar in letrozole-induced PCOS in female Wistar rats:

1. After 28 days repeated dose of Saroglitazar (4 mg/kg, PO) significantly reduced number of cystic follicles in Letrozole-treated female rats when compared with vehicle control.

In second study, female Zucker fa/fa rats of 13-15 weeks were used. Zucker fa/fa rats are genetically obese, hyperinsulinemic and hyperlipidemic. PCOS can be developed when manipulated surgically or by environmental modifications. Therefore, this model proves to be suitable for predicting the likely therapeutic benefit of novel treatment for PCOS in humans.

Following observations were recorded after repeated dose treatment with Saroglitazar in letrozole-induced PCOS in Zucker fa/fa rats.

1. Saroglitazar significantly improved insulin tolerance.
2. Saroglitazar significantly increased serum FSH levels, with little change in LH levels and reduced LH/FSH ratio.
3. Saroglitazar significantly decreased serum testosterone levels.
4. Saroglitazar significantly normalized ovary weight.

In conclusion, repeated dose oral treatment with Saroglitazar at 4 mg/kg resulted in significantly improved insulin sensitivity, increased serum FSH, decreased LH/FSH ratio, decreased serum testosterone and normalized ovary weight.

Clinical Experience

Maximum Tolerated Dose in Phase 1 was 16 mg/day for 10 days and it was found to be well tolerated. In Phase 1 trials in healthy human volunteers, Saroglitazar Magnesium was found to be well tolerated in single [12] and multiple dose studies without any safety concern. Several Phase 2 studies were conducted to evaluate the safety and efficacy of Saroglitazar Magnesium in dyslipidemic subjects without diabetes, diabetes and subjects with impaired glucose tolerance test.

In dyslipidemic subjects with diabetes mellitus, Saroglitazar Magnesium showed favorable results in all the expected endpoints (fasting plasma glucose: (FPG) and lipid profile). Saroglitazar Magnesium, especially 2 mg Saroglitazar Magnesium and 4 mg Saroglitazar Magnesium seemed to be comparable to Pioglitazone and Rosiglitazone and showed clinically relevant reduction in the triglyceride-cholesterol (TG-C), total cholesterol and FPG levels.

A Phase 3 study of 24-week duration to evaluate the efficacy and safety of Saroglitazar Magnesium in diabetic dyslipidemic patients as compared to Pioglitazone revealed that there is statistically significant reduction in the TG-C levels at all visits as compared to baseline in Saroglitazar Magnesium 2 mg and 4 mg groups. There was statistically significant reduction (45%) in the TG-C levels in Saroglitazar Magnesium 4 mg Tablets as compared to Pioglitazone 45 mg (15.5%). Similarly there was statistically significant reduction (45.5%) in the very-low-density lipoprotein (VLDL) cholesterol and total cholesterol levels (7.7%) as compared to Pioglitazone.[10]

A Phase 3 study of 12-week duration to evaluate the efficacy and safety of Saroglitazar Magnesium in diabetic dyslipidemic patients not controlled with atorvastatin 10 mg revealed statistically significant reduction (>45%) in the TG-C levels as compared to placebo. Statistically significant reduction in the LDL cholesterol (>27.5%), total cholesterol (>22%) and apo B (>27%) levels with Saroglitazar Magnesium 4 mg Tablets was observed as compared to baseline. Thus far, Saroglitazar Magnesium clinical studies have shown efficacy in patients with mild to moderate dyslipidemia and showed favorable effects.[11]

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

2.4 RISK AND BENEFIT

The safety and tolerability of Saroglitazar Magnesium is well defined on the basis of pre-clinical and clinical studies (Phase 1 to Phase 3). [redacted] Saroglitazar Magnesium is approved in India at the doses of 2 mg and 4 mg QD for treatment of "diabetic dyslipidemia" and "hypertriglyceridemia with type 2 diabetes mellitus (T2DM) not controlled by statin therapy". In addition, since insulin resistance, obesity and MS are common features of both NAFLD and PCOS, it is very likely that

NAFLD and PCOS coexist in a given set of patients. There are a number of important knowledge gaps in the field of PCOS and NAFLD. These can be broadly categorized into (a) prevalence and clinical risk factors for NAFLD in women with well characterized PCOS; (b) spectrum of liver disease severity, characterized non-invasively and when possible invasively; (c) mechanistic basis for prevalence and severity of NAFLD; and (d) novel treatments. However, very limited clinical data are available in patients of PCOS with NAFLD. This proof-of-concept phase 2A study will evaluate the concept of efficacy of Saroglitazar Magnesium 4 mg Tablets once-daily in women with well characterized PCOS diagnosed with NAFLD. If efficacy and safety are shown, that will provide a strong basis for long term evaluation of decreasing the disease burden for patients with PCOS and NAFLD.

3 STUDY OBJECTIVES

Objective:

The purpose of this study is to evaluate the efficacy and safety of Saroglitazar Magnesium 4 mg Tablets once-daily in women with well characterized PCOS diagnosed with NAFLD.

3.1 PRIMARY OBJECTIVE

To evaluate the effect on hepatic fat content, measured as proton-density fat-fraction (PDFF) by magnetic resonance imaging (MRI), of once-daily Saroglitazar Magnesium 4 mg Tablets for 24 weeks vs placebo.

3.2 SECONDARY OBJECTIVES

- To assess the effect of a 24-week treatment regimen of once-daily Saroglitazar Magnesium 4 mg Tablets on the following parameters in patients of PCOS with NAFLD:

  1. Liver enzymes/LFTs.
  2. Insulin resistance measured by Homeostasis Model Assessment (HOMA).
  3. Liver stiffness measurement obtained via transient elastography/FibroScan®.
  4. Controlled attenuation parameter obtained via transient elastography/FibroScan®.
  5. Body weight, BMI and waist circumference.
  6. MRI-derived total liver fat index and total liver volume.
  7. Serum lipid profile and lipoproteins.
  8. Sex hormone binding globulin.
  9. Ovarian function.
  10. Free androgen index.
  11. Pharmacokinetics of Saroglitazar following first dose and last dose.

3.3 SAFETY ASSESSMENT

Criteria for Safety:

1. Vitals: blood pressure (BP) (sitting BP after 05 min rest; systolic and diastolic BP), pulse rate, oral temperature and respiratory rate (at Visit 1[Screening] and at Visit 3 through Visit 8 [End-of-Treatment]).

2. Body mass index at Screening Visit (Visit 1), at 12 weeks (Visit 6) and at the Week 24 End-of-Treatment visit (Visit 8).

3. Waist measurements at Screening Visit, at Visit 6 and at the End-of-Treatment visit.
4. The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, pelvic, breast, chest, heart, lungs, abdomen, skin, extremities, neurological systems,

musculoskeletal systems and weight measurement. Investigator should also evaluate the patients for hirsutism and virilizing signs (upper lip, chin, chest, upper abdomen, lower abdomen, thighs, back, arm and buttocks). Note: Breast examination will be done as part of screening. Pelvic examination will be performed as part of screening, if not performed within 6 months of randomization.

5. Laboratory assessment:

    a. Hematology: Hematocrit, hemoglobin, mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, mean platelet volume, red blood cell (RBC) count, white blood cell (WBC) count, differential WBC count.

    b. Liver enzymes/LFTs: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (with conjugated bilirubin), gamma glutamyltransferase (GGT), serum protein and albumin.

    c. Renal function tests (RFTs): blood urea nitrogen (BUN), creatinine and estimated glomerular filtration rate (eGFR). Estimated glomerular filtration rate will be calculated by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

    d. Inflammatory marker: high sensitivity C-reactive protein (hs-CRP).

    e. Lipid profile and lipoproteins: triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), small dense low-density lipoprotein (sdLDL), very low density lipoprotein (VLDL), free fatty acids, apolipoprotein A and apolipoprotein B.

    f. Urine examination: physical examination (appearance, color, specific gravity and pH); microscopy (epithelial cells, red blood cells, pus cells, cast and crystals) and chemical examination (protein, glucose, bilirubin, urobilinogen, ketone bodies and nitrite).

    g. T3, T4 and thyroid stimulating hormone (TSH)

    h. Serum pregnancy test

    i. Urine pregnancy test

    j. Serology: HIV type 1 and type 2, hepatitis A virus (HAV), anti-hepatitis B virus surface antigen (HBsAg) and hepatitis C virus (HCV) (at Visit 1).

    k. International normalized ratio (INR) and prothrombin time (PT)

    l. Cytokeratin 18

m. Free androgen index and SHBG level

n. Total testosterone and free testosterone

o. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels

p. 17-hydroxyprogesterone

q. Estradiol

r. Creatine Kinase (CK)

s. Cardiac function: 12-lead-electrocardiogram (ECG)

t. Glycemic control: FPG, HbA1c and plasma insulin levels.

u. B-type natriuretic peptide (BNP) and aminoterminal fragment of BNP prohormone (NT-proBNP)

v. Papanicolaou (PAP) test

w. Cardiac troponin, creatine kinase-muscle/brain (CK-MB)

x. Lipase and amylase

y. Uric acid

6. Adverse event(s): Frequency and severity of AE /serious adverse events (SAEs), drop-outs due to AEs/SAEs for all subjects enrolled will be recorded. All AEs, will be assessed using Council for International Organizations of Medical Sciences (CIOMS) criteria using:
    a. Causality
    b. Severity
    c. Seriousness
    d. Expectedness

Note: Efficacy assessments and laboratory assessment (liver fat content by MRI-PDFF [MRI-PDFF will be performed during screening phase, screening phase results will be used as the baseline assessment], controlled attenuation parameter, hormonal profile, fasting plasma glucose, lipid and lipoprotein profiles, MRI-derived total liver fat index and total liver volume [MRI-derived total liver fat index and total liver volume assessment will be performed during screening phase, screening phase results will be used as the baseline assessment**]**, plasma insulin levels, homeostasis model assessment (insulin resistance [HOMA-IR]), liver stiffness by transient elastography/FibroScan®, ovarian function, liver enzymes/LFTs, hematology, coagulation test (PT/INR), renal function test, CK, hs-CRP, BNP , NT-proBNP, cardiac troponin, CK-MB, lipase and amylase, TNFα, uric acid, TSH, T3 and T4, serology, HIV type 1 and type 2, HAV, anti-

HBsAg, HCV, serum pregnancy test, urine microscopy and urine chemistry) which will be done at Visit 1 will be considered for baseline visit. PAP test, endometrial biopsy and mammography will be performed as per Time and Events Schedule.

4 STUDY POPULATION

Patients of PCOS with NAFLD will be recruited for this study.

4.1 NUMBER OF SUBJECTS PLANNED

A total 90 subjects (including 20% dropouts), will be enrolled across USA and Mexico in a ratio of 1:1 to have 45 subjects in each treatment arm i.e., Saroglitazar Magnesium 4 mg Tablets and placebo. Additional patients will be enrolled if the dropout rate is more than 20%.

Six patients in each group are planned for pharmacokinetic assessment therefore a total of 12 patients will be included. Additional patients may be enrolled into the study to ensure that the pharmacokinetic assessment is performed on at least 6 completed patients in each treatment arm.

4.2 INCLUSION CRITERIA

1. Females, 18 to 45 years of age.
2. Previously confirmed diagnosis of PCOS by Rotterdam criteria[17] (at least 2 of 3):
   1) oligo-and/or anovulation;
   2) hyperandrogenism (clinical and/or biochemical);
   3) polycystic ovary morphology on ultrasonography (either 12 or more follicles measuring 2–9 mm in diameter or an increased ovarian volume >10 cm^3).
3. Evidence of NAFLD within 6 months prior to the Screening Visit (Visit 1). The diagnosis of NAFLD is made according to the American Association for the Study of Liver Diseases criteria.[18]

   a) hepatic steatosis by imaging or histology,

   b) no significant alcohol consumption,

   c) no competing etiologies for hepatic steatosis, and

   d) no co-existing causes for chronic liver disease.

4. Alanine transaminase ≥ 38 U/L at Visit 1. Visit 2 ALT must not increase >30% from Visit 1.
5. Hepatic fat fraction ≥10% by MRI-PDFF.
6. Willingness to participate in the study.
7. Ability to understand and give informed consent for participation.
8. A normal pelvic examination within past 6 months before randomization.
9. A normal breast examination at screening (If Mammogram has been done in the preceding 12 months it will be documented. If patient is not up to date with standard breast cancer screening guidelines and is willing to receive screening, mammogram

will be offered prior to enrollment as part of standard care).

10. A normal Papanicolaou (PAP) test within past 6 months before randomization (If PAP test has not been performed within 6 months of the screening visit, it must be performed during screening).
11. Woman who agrees to use the following contraceptive methods:
    a. Combination hormonal contraceptives (including pills, patches and vaginal rings).

    For the following conditions, the usage of the combination hormonal contraceptives should be based upon a discussion with the subject and the investigators' clinical judgment.

    i. Women greater than 35 years of age who also smoke fewer than 15 cigarettes per day
    ii. Adequately controlled hypertension
    iii. Properly taken blood pressure above a systolic 140-159 mm Hg or diastolic 90-99 mm Hg
    iv. Known hyperlipidemia
    v. Diabetes associated with vascular disease, including neuropathy, retinopathy and nephropathy.
    vi. Diabetes duration greater than 20 years.

    b. Women with the following conditions should use effective methods other than combined hormonal contraceptives (e.g., Progestogen-only oral contraceptives or progestogen-containing intrauterine devices (IUD), Non-hormonal IUD, Double-barrier contraception [e.g., condom plus diaphragm]):

    i. Women greater than 35 years of age who also smoke 15 or more cigarettes per day
    ii. Properly taken blood pressure above systolic ≥ 160 mm Hg or diastolic ≥ 100 mm Hg
    iii. Known hyperlipidemia
    iv. Vascular disease, including neuropathy, retinopathy and nephropathy
    v. Diabetes duration greater than 20 years.

4.3 EXCLUSION CRITERIA

1. Presence of other chronic liver diseases (hepatitis B or C, autoimmune hepatitis, cholestatic liver disease, Wilsons disease, hemochromatosis, etc.).
2. Average alcohol consumption ≥ 7 drinks per week for women in the 6 months prior to enrollment. Subjects will be required to have an "Alcohol Use Disorder Identification Test" (AUDIT) score of <8.
3. Clinical, imaging, or histological evidence of cirrhosis.
4. Any of the following laboratory values:
    a. Hemoglobin <10 g/dL
    b. White blood cell count <4 x 10^9/L
    c. Neutrophil count <1.5 × 103/µL
    d. Abnormal baseline platelet counts (<150 x 10^3 uL).

e. Total Serum bilirubin greater than the ULN (>1.3 mg/dL) (except in patient with known Gilbert Syndrome where TB up to 2.5 mg/dL is allowed)
f. Albumin <3.2 g/dL
g. Serum ALT or AST >250 IU/L
h. Lipase or amylase more than the ULN at baseline.
i. Serum creatinine ≥1.5 mg/dL
j. Renal impairment as demonstrated by baseline estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated using the CKD-EPI equation).
k. Total creatine kinase level more than the ULN at baseline.

5. Patient with INR >1.3
6. Patients who have used medications known to cause hepatic steatosis (e.g., corticosteroids, amiodarone, methotrexate, tetracycline, tamoxifen, anabolic steroids, or valproic acid) for more than 2 weeks in the past year.
7. Prior bariatric surgery.
8. Weight loss of more than 5% in the 3 months preceding screening.
9. Severe co-morbidities (e.g., advanced cardiac, renal, pulmonary, or psychiatric illness).
10. Known allergy, sensitivity or intolerance to Saroglitazar Magnesium, comparator or formulation ingredients (Saroglitazar Magnesium Micronized, Magnesium Oxide Light, Microcrystalline Cellulose, Anhydrous Lactose, Croscarmellose Sodium, Povidone k 30, Talc (luzena c), Colloidal Silicon Dioxide and Magnesium Stearate).
11. Use of antidiabetic and lipid lowering medications if the dose is not stable for at least the 3 months preceding screening.
12. Intake of Vitamin E (>100 IU/day) or multivitamins containing Vitamin E (>100 IU/day) 3 months before enrollment.
13. Use of drugs with potential effect on NAFLD/NASH such as S-adenosylmethionine (SAM-e), Betaine, Pentoxifylline, Thiazolidinediones (Pioglitazone, Rosiglitazone), Obeticholic Acid or Milk Thistle in the 3 months prior to screening.
14. Changing doses of statins (Simvastatin, Pravastatin, Atorvastatin, Fluvastatin, Lovastatin, Rosuvastatin) or Fibrates (Clofibrate, Fenofibrate) in the 3 months prior to enrollment.
15. Illicit substance abuse within the past 12 months.
16. Pregnant or breast-feeding females.
17. Poorly controlled diabetes with HBA1c >8.5%
18. Use of total parenteral nutrition in the 6 months preceding enrollment.
19. Women with known Cushing syndrome or hyperprolactinemia.
20. Late onset congenital adrenal hyperplasia, androgen-producing tumors.
21. Refusal or inability to comply with the requirements of the protocol, for any reason, including scheduled clinic visits and laboratory tests.
22. History of myopathies or evidence of active muscle diseases.
23. History or current significant cardiovascular disease, including:
    i. Unstable angina (i.e., new or worsening symptoms of coronary heart disease within the past 3 months before screening), acute coronary syndrome within the past 6 months before screening, acute myocardial infarction in the past 3 months or heart

failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months before screening.

ii. History or current unstable cardiac dysrhythmias within prior 3 months before screening.

iii. Uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg).

iv. Stroke or transient ischemic attack prior 6 months before screening visit.

24. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer.
25. History of bladder disease other than urinary tract infection or cystitis. Previous or current hematuria due to etiologies other than urinary tract infection or kidney stones.

4.3.1 Screen Failures

Patients who fail the screening criteria will not be rescreened unless approved by the Sponsor or its designee. Screening laboratory tests may be repeated following the approval of Sponsor or its designee if the laboratory test results seem implausible or inaccurate.

A screen failure occurs when a patient who has signed the informed consent form (ICF) does not meet all the entry criteria outlined in this protocol and has not been randomized or received study drug. No study procedures (including end-of-treatment procedures) will be performed for these patients. For patients who fail to meet the inclusion criteria or who meet 1 or more of the exclusion criteria, the Principal Investigator (PI) (or designee) will document on a screening log the reason for the screening failure.

4.4 PATIENT WITHDRAWAL

Patients may withdraw from the entire study at any time without penalty and for any reason without prejudice to her future medical care. Although a patient is not obliged to give her reason for withdrawing prematurely, the PI will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the PI for follow-up of AE(s) as detailed in Section 9.4.1.6. Every effort will be made to continue clinical and/or laboratory follow-up, as appropriate, in patients who wish to withdraw from the study drug (Investigational product or placebo) and reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that she is in satisfactory health. A patient's withdrawal of consent and agreement to undergo a final examination will be documented on the electronic case report form (e-CRF).

As far as possible, all assessments scheduled for end-of-treatment must be performed on all patients who receive the study drug but do not complete the study according to protocol. In addition, if patient withdraws from the study, any data collected during the period of time will maintained as part of the study data.

4.4.1 Discontinuation of Patients from the Study or Study Drug

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

- Noncompliance to the protocol requirements.
- Occurrence of a serious or intolerable AE and based upon the Investigators' clinical judgment.
- The Sponsor or PI terminates the study (Section 4.6).
- Either the PI or the Sponsor decides that discontinuing the study or discontinuing the patient is in the patient's best interest.
- For reasons related to safety as specified in Section 4.5.
- The patient is lost to follow-up.
- A patient may also be discontinued from study drug/study by the Sponsor, Regulatory Authorities or Institutional Review Board (IRB) or Independent Ethics Committee (IEC).
- If the patient becomes pregnant.

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

Every effort will be made to continue clinical and laboratory follow-up, as appropriate, in patients who are withdrawn or in whom the study drug is stopped by the PI or per individual stopping rules (Section 4.5).

4.4.2 Patients Lost to Follow-up

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

4.5 STOPPING CRITERIA FOR INDIVIDUAL PATIENTS

The following clinical events warrant discontinuation of study drug; however, the patient will continue to be followed for safety, hormonal profile, 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) grade 3 or higher that is possible or probable drug related and discontinue any patient with an AE of CTCAE grade 4 or higher regardless of attribution to drug.

- Serious AE that may be related to the drug and warrant discontinuation as per discretion of the PI.

- In the opinion of the PI, continuation of study drug poses a health risk to the patient.

- Evidence of drug induced liver injury requiring study drug discontinuation as shown in the algorithm below.

- The second LFTs [AST, ALT, ALP, GGT, serum protein, albumin and total bilirubin (with conjugated bilirubin)] values during the Screening Phase (those obtained at Visit 2) will be considered as baseline for the safety assessment.

    - If patients with abnormal baseline liver indices develop elevations of AST or ALT greater than 2 times baseline or total bilirubin greater than 1.5 X baseline values (BL) while on study, testing should be repeated within 48-72 hours. If there are persistent elevations in ALT or AST greater than 2 X baseline or TB greater than 1.5 X baseline values, then close observation (see DILI Guidance for definition, testing and physical examination 2-3 times per week) should be initiated or drug should be discontinued.

    - A decision to discontinue or temporarily interrupt a study drug should be considered based on factors that include how much higher baseline ALT and AST were relative to the upper limit of normal (ULN) and how much the on study ALT and AST levels have increased relative to baseline, in addition to whether there is concomitant elevation of bilirubin or INR.

    - The criteria for discontinuing or temporarily interrupting study drug are as follows:

        - When the baseline values were ≥ 1.5 X ULN but < 5 X ULN, discontinue if ALT or AST increases to > 3 X baseline.
        - Discontinue if ALT or AST increase > 2 X baseline and the increase is accompanied by a concomitant TBL increase to > 2 X baseline 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, 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.

- Total CK > 5X ULN
- Amylase or lipase > ULN
- eGFR < 60 ml/min/1.73 m^2 and where the value is reconfirmed after 24 hours. Additionally, any subject who requires renal replacement therapy should also be discontinued from drug.
- Complete Blood Counts: Hemoglobin < 10 g/dL or HCT < 30%; platelets < 100,000/microL; WBC < 4 x 10^9/L.

4.6 TERMINATION OF THE CLINICAL STUDY

If the Investigator, the Sponsor or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the clinical study continues, then the clinical study may be terminated after appropriate consultation among the involved parties. Also, the clinical study may be terminated at the Sponsor's discretion in the absence of such a finding. Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant or unacceptable risk to the patients enrolled in the clinical study;
- Three patients develop the same AE of CTCAE grade 3, considered to be at least probably related to study drug;
- Two patients develop any AE of CTCAE grade 4, considered to be at least probably related to study drug;
- One patient develops an AE of CTCAE grade 5, considered to be at least probably related to study drug;
- Failure to enroll patients at the required rate;
- A decision of the Sponsor to suspend or discontinue development of the study drug.

Should the study be terminated and/or the site closed for whatever reason, a copy of all documentation pertaining to the study and study drugs must be returned to the Sponsor. All the site specific documents will be archived at study site.

5 STUDY TREATMENTS / INVESTIGATIONAL PRODUCT MANAGEMENT

Saroglitazar Magnesium 4 mg Tablets or placebo will be administered in patients of PCOS with NAFLD once daily in the morning before breakfast without food, for a period of 24 weeks.

5.1 TREATMENTS TO BE COMPARED

5.1.1 Investigational Product Description

The products that will be used in this study are outlined in Table 2.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]0*
***Round-up quantity**					

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 Micronized (Refer section 5.1.1 for excipients details). The IP will be manufactured following current-Good Manufacturing Practice (cGMP) guideline.

5.2 DOSAGE AND TREATMENT SCHEDULE

Patients will receive either 4 mg Saroglitazar Magnesium or placebo orally once each morning before breakfast without food, for 24 weeks during the double-blinded treatment period. However, on scheduled visits patients will have the IP administered on site after the blood sample collection. The drug dose during the treatment phase, this will be checked and verified with study medication compliance by using drug accountability form.

5.3 PACKAGING, LABELLING AND SUPPLY

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

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

5.4 STORAGE CONDITIONS AND STABILITY

Investigational product will be stored at room temperature (20°C to 25°C or 68°F to 77°F) and in dry place, protected from light. If the IP temperature extends outside the 20-25°C range, a temperature excursion must be documented in IP specific temperature log. 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 15-30^{o} C it will be considered as a protocol deviation. Storage condition will be maintained during shipment. All IP supplies in the study will be stored in a secure location with access limited to the Site Pharmacist or the Investigator designated site staff.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug preparation, handling and storage.

5.5 BLINDING

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

The blind must only be broken following 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 scratchcard 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 PATIENTS TO THE TREATMENT GROUPS

Patients will be randomly assigned in a 1:1 ratio to Saroglitazar Magnesium 4 mg Tablets and 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 is known to safely and effectively improve dyslipidemia by reducing TG, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol, non-high-density lipoprotein (non-HDL) cholesterol and increasing HDL cholesterol. In addition, Saroglitazar Magnesium can improve glycemic indices in diabetic patients by reducing fasting serum glucose and glycated hemoglobin. Considering the association between insulin resistance, dyslipidemia and the development of NASH, Saroglitazar Magnesium could potentially benefit patients with NAFLD including those with NASH and PCOS.

Saroglitazar Magnesium 4 mg Tablets have favorably modified the lipid profile in dyslipidemic and hypertriglyceridemic patients during previously conducted Phase 2 and 3 studies.[10, 13] Based on these results, Saroglitazar Magnesium 4 mg dose has been selected for this study.

5.8 CONCOMITANT THERAPY

All medications received by the subject at any time prior to the Screening Visit and taken within 3 months before the Screening Visit, during the interval between the Screening Period and Randomization and those taken throughout the trial will be recorded on the appropriate section of the eCRF. The site may rely on subject reports for this information. All subjects must be questioned about concomitant medication at each visit. All concomitant medication, both prescribed and over-the-counter, must be recorded in the eCRF. This includes drugs used on a chronic and as needed basis. Medications that are indicated as prohibited in the Exclusion Criteria must not be used after the Screening Visit during the interval between the screening period and randomization or during the trial.

The following treatment/drugs will be allowed during the study.

- Treatment for common illness during the study may be allowed.

- Stable antidiabetic and lipid lowering medications at least for the 3 months preceding screening.

- Stable doses of metformin or any treatment of PCOS at least for the 3 months preceding screening.

- For any required concomitant medication, the patient must be on a stable dose for 3 months at study entry and patients must continue with their current drug regimen without any change in dosage.

5.8.1 Subjects on Concomitant Anti-diabetic Medication

Subjects on anti-diabetic medication shall also be assessed at scheduled visits for hyperglycemia/hypoglycemia; rescue medication will also be permitted, if required. Patients on concomitant anti-diabetic medication will be provided with a glucometer and instructions for use. All point of care (POC) glucose measurements by the patient during the study period should be performed on the study provided glucometer. The investigational site will download/record the data from glucometer for assessment of glucose levels since the prior visit.

The patients should monitor their glucose levels as follows:

- Fasting blood glucose should be measured on at least two days in a week. These measurements should be done in the morning before having breakfast and when the subject has been fasting for a minimum of 10 hours.

- Spontaneous measurements of the blood glucose should be done in the event the patient suffers from suspected hypoglycemia. The investigator should inform the patients on recognizing the symptoms of hypoglycemia (i.e. palpitations, tremor, diaphoresis, hunger and/or cognitive impairment) and instruct them on the actions to be taken in accordance with standard-of-care.

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

1. Consume 15-20 grams of glucose or simple carbohydrates

2. Recheck your blood glucose after 15 minutes

3. If hypoglycemia continues, repeat #1 & #2

4. Once your blood glucose returns to a normal level, consume a small snack if your next planned snack or meal is greater than 1 hour in the future

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

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

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

Investigators shall advise subjects to report any/all hypoglycemic episodes occurring during the course of the trial as they will be recorded in the eCRF.

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

5.8.2 Previous and Concomitant Medications

Any medication the patient takes other than the study drug, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications and any changes in the dosage or regimen of a concomitant medication for the 3 months preceding visit 1 until the end of the study (i.e., the safety telephone call) must be recorded in the eCRF.

5.8.3 Excluded Concomitant Medications

Patients are not permitted to take the following medications:

- Zileuton, parenteral nutrition and Vitamin E (>100 IU/day)

- Other drugs with potential effect on NAFLD such as Ursodeoxycholic acid, SAM-e, Betaine, Pentoxifylline, or Milk Thistle.

- Thiazolidinediones (pioglitazone, rosiglitazone), chemotherapy or other investigational medications during the study duration.

- Patients are not permitted to take medications which causes hepatic steatosis (e.g., corticosteroids, amiodarone, methotrexate, tetracycline, tamoxifen, anabolic steroids, or valproic acid).

- The known CYP2C8 inhibitors/substrates are not permitted during the study (Appendix 1: List of Known CYP2C8 Inhibitors/Substrates).

- Patients are not permitted to take medications such as digoxin, warfarin, quinidine, prazosin, etc.

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

The doses of statins (simvastatin, pravastatin, atorvastatin, fluvastatin, lovastatin, rosuvastatin) or fibrates (clofibrate, fenofibrate) should remain stable throughout the study period as much as possible.

5.8.3.1 Permitted Concomitant Medications

With the exception of excluded concomitant medications, other medications that patients have been taking at stable dosages for at least 3 months preceding visit 1, i.e., lipid lowering drugs and drugs for glycemic control, will be permitted as concomitant medications, including antidiabetic drugs such as metformin, sulfonylureas, dipeptidyl peptidase 4 inhibitors and insulin. To the extent possible, patients should continue with their current regimen of medication without any change throughout the study. Allowed over-the-counter medications include acetaminophen (maximum 1 gram/day), ibuprofen (maximum 800 mg/day) or naproxen (maximum 440 mg/day) or antacids such as H2 receptor blockers or proton-pump inhibitors for shorter duration as per investigator discretion.

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

5.8.4 Other Restrictions

5.8.4.1 Alcohol

Patients are encouraged to stop alcohol consumption entirely during the trial. They are not permitted to consume ≥7 drinks per week of alcohol before 6 months prior to enrollment and during the study. Alcohol consumption will be recorded throughout the study period.

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

Saroglitazar Magnesium 4 mg Tablets or placebo will be administered by qualified staff at scheduled site visits and the details administration will be recorded in the eCRF.

Investigator or designated study personnel will maintain a log of all study drugs dispensed to a study patient and returned to the site by the study patient into the eCRF for the purpose of drug supply management and accountability. If Saroglitazar Magnesium 4 mg Tablets or placebo will be administered outside of the study site (at-home use/self-administration), subjects will be instructed regarding storage of study drug at-home use/ self-administration. In addition, all unused study drug shipped back to the Sponsor/drug suppliers will be captured on a drug accountability form, of which a copy will be included with the shipment and a copy retained in the study records. 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 EFFICACY

6.1.1 Primary Endpoint

Change in hepatic fat content from baseline following 24 weeks of treatment as measured by MRI-PDFF.

6.1.2 Secondary Endpoints

1. Changes from baseline to Week 12 and Week 24 in liver enzymes/LFTs: ALT, AST, ALP, GGT, serum protein, albumin and total bilirubin.
2. Changes from baseline to Week 12 and Week 24 in insulin resistance as measured by HOMA.
3. Changes from baseline to Week 24 in markers of liver injury and fibrosis including CK-18, hs-CRP, TNFα, and liver stiffness measured by transient elastography/FibroScan®.
4. Changes from baseline to Week 24 in controlled attenuation parameter measured by transient elastography/ FibroScan®.
5. Changes from baseline to Week 12 and Week 24 in body weight, BMI and in waist circumference.
6. Changes from baseline to Week 24 in MRI-derived measures of total liver fat index and total liver volume.
7. Changes from baseline to Week 12 and Week 24 in lipid and lipoprotein levels: TG, TC, HDL, LDL, sdLDL, VLDL, apolipoprotein A and apolipoprotein B.
8. Changes from baseline to Week 12 and Week 24 in SHBG level.
9. Changes from baseline to Week 12 and Week 24 in ovarian function (Total testosterone, 17-hydroxyprogesterone, free testosterone, luteinizing hormone, follicle-stimulating hormone, LH-to-FSH ratio and estradiol).
10. Changes from baseline to Week 12 and Week 24 in free androgen index.
11. Pharmacokinetics of Saroglitazar following first dose and last dose.

6.2 SAFETY

1. Adverse event(s): frequency and severity of AE/SAEs, drop-outs due to AEs/SAEs for all subjects enrolled will be recorded. All AEs, will be assessed using CIOMS criteria which includes:
    - Causality
    - Severity
    - Seriousness
    - Expectedness
2. Clinical laboratory testing (hematology, clinical chemistry, hormonal profile and urinalysis).
3. Twelve-lead ECG.

4. Vital signs.
5. Physical examination (Physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, pelvic, breast, chest, heart, lungs, abdomen, skin, extremities, neurological systems, musculoskeletal systems and weight measurement. Investigator should also evaluate the patients for hirsutism and virilizing signs (upper lip, chin, chest, upper abdomen, lower abdomen, thighs, back, arm and buttocks). Note: Breast examination will be done as part of screening. Pelvic examination will be performed as part of screening, if not performed within 6 months of randomization.

6.2.1 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 ECGs, may signify an adverse finding. Additional examinations or repetition of test will be performed as medically indicated. If the Investigator considers the abnormality as of major 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), then this diagnosis should be recorded as AE. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

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

For any abnormal test result that meets one of the above conditions except for the last condition, the Investigator will provide a justification for not reporting the abnormal test finding as an AE. Each AE shall be evaluated for the severity, duration, resolution, action taken and its association with the study treatment. The study participant may be withdrawn or terminated from the study depending on the seriousness of the adverse effects.

6.2.2 Appropriateness of Measurement

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

7 INVESTIGATIONAL PLAN

7.1 STUDY DESIGN AND PLAN

This is a multicenter, phase 2A, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Saroglitazar Magnesium in women with well characterized PCOS, 18-45 years of age diagnosed with NAFLD. A total 90 subjects (including 20% dropouts), will be enrolled across USA and Mexico in a ratio of 1:1 to have 45 subjects in each arm i.e., Saroglitazar Magnesium 4 mg Tablets and placebo. Six patients in each group are planned for pharmacokinetic assessment therefore a total of 12 patients will be included.
The study will be conducted over a period of up to 34 weeks. Subjects will be evaluated at study sites for 8 scheduled visits: (Visit 1: Day [-28]), Visit 2: Day [-14 to -7]), randomization (Visit 3: Week 1, Day 1), Visit 4 (Week 2, Day 14), Visit 5 (Week 8, Day 56), Visit 6 (Week 12, Day 84), Visit 7 (Week 16, Day 112) Visit 8 (Week 24, Day 168). After completion of the study treatment period, the subjects will be followed for an additional period of 6 weeks without study medication until Visit 9 (Week 30, Day 210).

7.2 STUDY PROCEDURES AT EACH VISIT

Time and Events Schedule for the trial is given in Table 1.

Pre-screening Visit: An informed consent will be obtained from the potential subjects before any pre-screening evaluations. The study sites may identify potential subjects by conducting a laboratory evaluation of the ALT levels. This optional pre-screening can be conducted before the actual study screening. A subject with an ALT ≥38 U/L may be considered for the actual study screening. Also, along with the evaluation of the ALT levels, in those potential subjects who do not have a documented diagnosis of NAFLD through any imaging method, an optional abdominal ultrasound or Fibroscan® may be performed during the pre-screening.

In addition, an optional lab evaluation for diagnosis of PCOS through lab or ultrasound may be performed during pre-screening. The evaluation of the ALT levels during the pre-screening will be done at the local laboratory, whereas the laboratory evaluations during the screening and the treatment phase will be done at the central laboratory.

Screening Phase

Visit 1 (Day -28): In this study, the screening phase will consist of 28 days. Unless otherwise specified, screening procedures may be completed at any time during the screening period. Before each patient is enrolled to the study, informed consent will be obtained from the patient (or her legally authorized representative) according to the regulatory and legal requirements of the participating country. Patient eligibility for participation in the study will be assessed. Current social, medical and ovarian dysfunction history will be obtained and physical examination, vital signs, ECGs, laboratory evaluations (including serology, hematology, lipid and lipoprotein profiles, liver enzymes/LFTs, BNP, NT-proBNP, cardiac troponin, CK-MB, lipase and amylase, hormonal profile and urinalysis) will be performed. PAP test, endometrial

biopsy and mammography will be performed as per Time and Events Schedule. Patients will undergo a serum pregnancy test. During this visit, subject will be seen by the investigator or designated study personnel and an AUDIT questionnaire will be administered.

Visit 2 (Day -14 to -7): Liver function tests (AST, ALT, ALP, GGT, total protein, albumin, total bilirubin (with conjugated bilirubin) will be re-measured approximately 2 weeks from Day -28 to determine eligibility.

Alanine transaminase ≥ 38 U/L at Visit 1. Visit 2 ALT must not increase >30% from Visit 1.

Randomization and Treatment Phase

Visit 3 to Visit 8: The randomization and treatment phase will include 6 outpatient visits (Visit 3 to Visit 8) over a period of 24 weeks including the randomization visit. All the eligible subjects will be randomly assigned into either of the two treatments arms: Saroglitazar Magnesium 4 mg Tablets and matching placebo tablets in a 1:1 ratio. Efficacy assessments will be conducted at 12 (hormonal profile, lipid and lipoprotein profiles, ovarian function and liver enzymes/LFTs) and 24 weeks visits (liver fat content by MRI-PDFF, hormonal profile, lipid and lipoprotein profiles, MRI-derived total liver fat index and total liver volume, homeostasis model assessment [insulin resistance (HOMA-IR)], liver stiffness by transient elastography/FibroScan®, controlled attenuation parameter, ovarian function and liver enzymes/LFTs). In addition, subjects will be monitored during the study and at every visit for development of any adverse events including drug induced liver injury. In addition to physical examination, laboratory data and ECGs done during the study period will be monitored to detect any treatment emergent adverse events.

Visit 3 (Week 1, Day 1): Patients will be randomly assigned to receive Saroglitazar Magnesium 4 mg Tablets or placebo orally once-daily, starting on Day 1 of a 24-week outpatient treatment period.

Visits 4, 5, 6, 7 and 8: Patients will visit the study site at Week 2 (Visit 4), Week 8 (Visit 5) Week 12 (Visit 6), Week 16 (Visit 7) and Week 24 (Visit 8) for clinical assessment, dispensation and reconciliation of study drug, measurements of efficacy endpoints and assessment of AEs.

Detailed efficacy and safety assessments are provided in Table 1 (Time and Events Schedule).

Safety follow-up visit (Visit 9): A final post-treatment visit will occur 6 weeks (±3 days) after the end-of-treatment visit for safety monitoring. A telephonic follow-up visit will be performed to assess any AE or SAE after the end-of-treatment visit for safety monitoring. As far as possible, all assessments scheduled for end-of-treatment must be performed on all patients who receive the study drug but do not complete the study according to protocol.

7.3 PHARMACOKINETIC ASSESSMENT

Twelve subjects will be included in the pharmacokinetic assessment. On study visit 3 (Day 1), and study visit 8 (Day 168) subjects will be asked to remain at the clinic for 10 hours after dosing. In addition, subjects may be remained in-house as per investigator discretion for a pharmacokinetic assessment. On these days, blood samples will be collected at the following timepoints: pre-dose (0.0), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 10.0 hours. Subjects will be asked to return to the clinic the following day for another collection approximately 24 hours after study drug administration on visit 3 (Day 1) and visit 8 (Day 168). In addition to these collections, pre-dose sample will be collected at visits 4 (Day 14), 5 (Day 56), 6 (Day 84) and 7 (Day 112). A detail pharmacokinetic laboratory manual will be prepared separately.

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

The pharmacokinetic parameters will be evaluated using Phoenix® WinNonlin® professional software (Version 8.0 or higher) for Saroglitazar and its metabolite Saroglitazar sulfoxide:

For Single Dose (i.e. for Visit 3)

i. Peak Plasma concentration (C_{max})

ii. Time to reach peak Plasma concentration (T_{max})

iii. Area under Plasma concentration vs. time curve till the last time point (AUC_{0-t})

iv. Area under Plasma concentration vs. time curve extrapolated to the infinity ($AUC_{0-\infty}$) after first dose

v. Area under plasma concentration vs. time curve in a 24 h dosing interval (AUC_{tau}) after first dose

vi. Elimination rate constant (K_{el})

vii. Elimination half-life (t_{Half})

viii. Apparent Volume of distribution (Vd/F)

ix. Apparent Clearance (CL/F)

Note: No value of Kel and related PK parameters will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. No value of Kel, AUCi, AUC_%Extrap_obs and tHalf will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

For Multiple Dose (i.e. for Visit 8)

i. Peak Plasma concentration ($C_{max,ss}$)

i. Time to reach peak Plasma concentration ($T_{max,ss}$)

ii. Area under plasma concentration vs. time curve in a 24 h dosing interval (AUC_{tau}) after last dose

iii. Elimination rate constant ($K_{el,ss}$)

iv. Elimination half-life ($t_{half,ss}$)

v. Apparent Volume of distribution ($Vd/F_{,ss}$)

vi. Apparent Clearance ($CL/F_{,ss}$)

vii. Minimal or Trough plasma concentration (C_{min})

viii. Fluctuation index.

ix. Accumulation index calculated as a ratio of AUC_{tau} (last dose)/AUC_{tau} (first dose)

Note: No value of $K_{el,ss}$ and related PK parameters will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

7.4 ADHERENCE TO PROTOCOL

Investigator shall strictly adhere to the protocol and Good Clinical Practice (GCP) guidelines. All subjects 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 subject may be withdrawn from the trial at the discretion of the Sponsor or the Investigator.

7.5 PROTOCOL DEVIATION

For the purposes of this study, no distinction will be made between Protocol Violations and Deviations. Deviations may be categorized as minor protocol deviation and a major protocol deviation. Minor protocol deviation includes any deviations that do not influence the outcome of the efficacy and safety endpoints. Minor protocol deviations do not require immediate notification to the IEC/IRB unless otherwise specified by IEC/IRB requirements. All minor protocol deviations will be noted in monitoring reports and provided to the investigator. Major protocol deviation includes any violation which may influence the outcome of the efficacy or safety endpoints. Major protocol deviations must be reported immediately to the IRB/IEC as specified by the IRB/IEC requirements. All Major protocol deviations will be reported to the Sponsor immediately. Note: persistent non-compliance of minor protocol deviations may rise to the level of major protocol deviations. The Sponsor reserves the right to terminate the study at a given center in the event of monitoring and/or auditing findings of serious or persistent non-compliance with the protocol, standard operating procedures (SOPs), GCP, and/or applicable regulatory requirement(s) by an investigator/institution. In all cases of site closure due to protocol deviations, the IEC/IRB and regulatory authority will be informed. The clinical study report will provide the list of protocol deviations/violations on separate section. Protocol deviation/violation will include but are not limited to the following;

- Subjects that did not meet entry criteria
- Subjects that developed withdrawal criteria but were not withdrawn
- Subjects that received the wrong treatment or incorrect dose
- Subjects that received an excluded medication

8 DATA MANAGEMENT AND BIOSTATISTICS

8.1 DATA MANAGEMENT

8.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Monitor during monitoring visits. The Monitor will verify data recorded in the electronic data capture (EDC) system with 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.

8.1.2 Computer Systems

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

8.1.3 Data Entry

Data must be recorded using the EDC system 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 Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

8.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

8.1.5 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 resolution through data queries. The eCRFs must be reviewed and electronically signed by the Investigator.

8.2 STATISTICAL DESIGN

Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock. The SAP will include detailed statistical aspects of the safety and efficacy analysis. Statistical analysis will be performed using SAS® (version 9.4 or higher) software (SAS Institute Inc., USA).

8.3 NULL AND ALTERNATIVE HYPOTHESIS

Below is the hypothesis of primary efficacy endpoint:

Null hypothesis: H_0: $S \leq P$

Alternative hypothesis H_1: $S > P$

Where: S = Treatment effect of Saroglitazar Magnesium 4 mg, P = Treatment effect of Placebo

Rejection of the null hypothesis will lead to the conclusion that the treatment effect of Saroglitazar Magnesium 4 mg is statistically significantly greater than the treatment effect of placebo group and hence the test drug is more effective than placebo.

8.4 STUDY POPULATION PLANNED ANALYSIS

8.4.1 Population

8.4.1.1 Safety population

Safety population will consist of all randomized patients who received at least 1 dose of study drug. All patients in the safety population will be analysed according to the actual treatment received.

8.4.1.2 Modified Intent-to-treat population (mITT)

The mITT population will consist of all randomized patients who received at least 1 dose of the study drug and have at least 1 post-baseline efficacy data.

Last observation carried forward method will be used as an imputation method for post-baseline missing values for mITT analysis.

8.4.1.3 Per-protocol population (PP)

The PP population is a subset of mITT population. The PP population will consist of all randomized patients completing the treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome (i.e., had both baseline and end-of-treatment MRI & has taken ≥80% and ≤120% of the study drug).

8.4.1.4 Pharmacokinetic population (PK)

Pharmacokinetic population will include all randomized patients with evaluable concentration profile and do not have any major protocol deviation(s) that could affect the PK profile of the treatment.

8.4.2 Planned Analysis

All efficacy analysis will be based primarily on the PP population and analysis based on mITT will be considered as supporting analyses for this proof of concept study.

The PP population is a subset of mITT population. The PP population will consist of all randomized patients completing the treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome (i.e., had both baseline and end-of-treatment MRI & has taken ≥80% and ≤120% of the study drug).

The mITT population will consist of all randomized patients who received at least 1 dose of the study drug and have at least 1 post-baseline efficacy data. Last observation carried forward method will be used as an imputation method for post-baseline missing values for mITT analysis.

8.4.2.1 Primary Efficacy Analysis

The primary analysis for the primary efficacy endpoint will be based on PP population. The primary efficacy endpoint in this study is the change in hepatic fat content from baseline following 24 weeks of treatment as measured by MRI-PDFF. The change from baseline of hepatic fat will be determined as (Week 24 value – Baseline value).

The primary endpoint will be summarized and change from baseline to Week 24 will be evaluated using ANCOVA model with treatment as factor and baseline value as covariate. Statistical significance will be tested at a one-sided p-value <0.025.

8.4.2.2 Secondary Efficacy Analysis

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

Following secondary endpoints will be analyzed:

1. Changes from baseline to Week 12 and Week 24 in liver enzymes/LFTs: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), Gamma-glutamyl transferase (GGT), serum protein, albumin and total bilirubin.
2. Changes from baseline to Week 12 and Week 24 in insulin resistance as measured by HOMA.

3. Changes from baseline to Week 24 in markers of liver injury and fibrosis including CK-18, hs-CRP, TNFα, and liver stiffness measured by transient elastography/FibroScan®.
4. Changes from baseline to Week 24 in controlled attenuation parameter measured by transient elastography/ FibroScan®.
5. Changes from baseline to Week 12 and Week 24 in body weight, BMI and in waistcircumference.
6. Changes from baseline to Week 24 in MRI-derived measures of total liver fat index and total liver volume.
7. Changes from baseline to Week 12 and Week 24 in lipid and lipoprotein levels: TG, TC, HDL, LDL, sdLDL, VLDL, apolipoprotein A and apolipoprotein B.
8. Changes from baseline to Week 12 and Week 24 in SHBG level.
9. Changes from baseline to Week 12 and Week 24 in ovarian function (Total testosterone, 17-hydroxyprogesterone, free testosterone, luteinizing hormone, follicle-stimulating hormone, LH-to-FSH ratio and estradiol).
10. Changes from baseline to Week 12 and Week 24 in free androgen index.
11. Pharmacokinetics of Saroglitazar following first dose and last dose.

The change from baseline will be determined as:

Change = (Post-baseline – Baseline)

Percent change will be calculated for all parameters except those measured in ratio or percent.
Percent Change = ((Post-baseline – Baseline) / Baseline) * 100

Treatment effects will be estimated using the least-square mean, standard error and 95% confidence interval from ANCOVA model with treatment as factor and baseline value as covariate. Treatment groups, Saroglitazar Magnesium 4 mg Tablets and placebo, will be compared using the difference in least-square means and p-values from the ANCOVA model.

Descriptive statistics will be provided for each Pharmacokinetic parameter as detailed in Section 7.3.

Above analysis will also be supported by simple summaries at each visit. 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 frequencies and percentages.

8.4.3 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 for each treatment group by visit. Summary statistics for clinical laboratory parameters, ECGs, physical examination and vital signs will be presented for each treatment 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 MedDRA (version 19 or higher) by treatment group, frequency, severity, seriousness, relationship to study drug and expectedness per System Organ Class and Preferred Term.

8.4.4 Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment and population set. Subject disposition and reason for withdrawal will be summarized and presented. 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 frequencies and percentages.

8.4.5 Interim Analysis

No interim analysis is planned for the study.

8.5 HANDLING OF MISSING DATA

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

Subjects who are discontinued from the study will be excluded from PP population. Any randomized subject who discontinued the study for any reason but have at least 1 post-baseline efficacy data will be included in the mITT population. Last Observation Carried Forward method will be used as an imputation method for the efficacy variables for mITT population.

8.6 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint of this study is the change from baseline in hepatic fat content at Week 24 as measured by MRI-PDFF. There is no data available on the change from baseline in hepatic fat content measured by MRI-PDFF.

A sample size of 74 completed subjects (37 subjects in each treatment arm) will provide 80% power to detect a 4% treatment difference in change from baseline in hepatic fat content at Week 24 between Saroglitazar 4 mg and Placebo using a two-sided 5% level of significance based on a two-sample t-test, assuming change from baseline in hepatic fat content of 9% at Week 24 in Saroglitazar 4 mg treatment arm with a common standard deviation of 0.6.

Assuming a 20% dropout rate at week 24, approximately 90 subjects will be randomized in a 1:1 ratio to receive either Saroglitazar 4 mg (45 subjects) or placebo (45 subjects). Additional subjects may be enrolled if the dropout rate is more than 20%. The sample size estimation was performed using PASS 14 software.

A total of 12 subjects, 6 subjects in each treatment arm will be included in the pharmacokinetic assessment.

Additional patients may be enrolled into the study to ensure the pharmacokinetic assessment is performed on at least 6 completed patients in each treatment arm.

8.7 RANDOMIZATION

Subjects will be randomly assigned in a 1:1 treatment allocation ratio to Saroglitazar Magnesium 4 mg Tablets 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).

9 ADMINISTRATIVE MATTERS

The trial will be carried out in compliance with the protocol, in accordance with the International Council for Harmonisation (ICH) guideline for GCP and in accordance with applicable regulatory requirements.

9.1 ETHICS

9.1.1 Institutional/independent Committee Review and Communications

The trial will not be initiated before the protocol and informed consent and subject information form have been reviewed and have received approval / favorable opinion from the IEC/IRB. Should a protocol amendment be made that requires 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 subjects may be implemented immediately provided that the appropriate regulatory authorities and IEC/IRB are notified as soon as possible and an approval is requested. Protocol amendments only for logistical or administrative changes may be implemented immediately; however, both the IRB/IEC and the Regulatory Authority 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 Investigator must provide the name and address of the central 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 subject participation in the trial, written informed consent will be obtained from each subject (or the subject's legally authorized representative) according to the regulatory and legal requirements of the participating country. Each signature must be dated by each signatory and the informed consent and any additional subject information form retained by the Investigator as part of the study records. A signed copy of the IEC/IRB approved informed consent and any additional subject information must be given to each subject or the subject's legally authorised representative.

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

Should a protocol amendment be made, the subject consent form and subject information form may need to be revised to reflect the changes to the protocol. It is the responsibility of the Investigator to ensure that an amended consent form is reviewed and received approval from the IEC/IRB, and to further ensure that it is signed by all subjects subsequently entered in the trial and those currently in the trial, if affected by the amendment.

9.2 RECORDS

9.2.1 Drug Accountability

The dispensing of study drug to the subject, and the return of the study drug from the subject, must be documented on drug accountability form. Subject or their legally authorized representative, must be instructed to return all the original containers, where empty or containing study drug. The subjects must return unused study drug to the site.

Receipt and dispensing of study drug must be recorded by an authorized person at the study site. The PI will maintain an accurate record of the receipt of the study drug as shipped by the Sponsor, including the date received. Study drug supply management will be processed and maintained on drug accountability forms, which will be monitored and reconciled by the study monitor assigned to the site. This inventory record must be available for inspection at any time. Copies of this record will be provided to the Sponsor at the conclusion of the study. The PI will not be allowed to store study drug at any site other than those listed on Form FDA 1572 or Investigator's Agreement or to dispense the study drug from sites not listed on this form. The PI will also agree that study drug will be dispensed by the PI or Sub-investigator named on Form FDA 1572 or Investigator's Agreement, or their qualified designees. The PI, Sub-investigators and qualified designees also agree that study drug will be dispensed only to study patients who have provided written informed consent and have met all entry criteria. Study drug may not be used for any purpose other than that stated in the protocol.

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

9.2.2 Emergency code break (Unblinding)

An emergency code break will be available to the investigator and / or pharmacist. This code break must only be opened in emergency situations when the identity of the study drug must be known by the investigator in order to provide appropriate medical treatment. If the code break for a subject is opened, Sponsor must be informed immediately. The reason for opening the code break must be documented along with the date and the initials of the person who broke the code.

Subjects whose treatment assignment becomes unblinded inadvertently, need not require to complete the scheduled evaluations and patient will be withdrawn from the trial from that visit.

9.2.3 Case Report Forms

All data generated by the site personnel will be captured electronically at each study center using eCRFs. Data from external sources (such as laboratory data) will be imported/entered into the database. Case reports forms must be kept current to reflect patient status at each phase during the course of trial. Patients are not to be identified on the case report form by name. Appropriate coded identification (e.g. Subject Number) and Patients initials must be used. The investigator must make a separate confidential record of these details (subject identification code list) to permit identification of all patients enrolled in a clinical trial in case follow-up is required. Relevant medical history will be documented at the screening visit. Thereafter during the trial narrative statements relative to the patient's progress during the trial will be maintained. See also 9.2.4. The investigator will be responsible for retaining all records pertaining to the trial as specified in the agreement.

9.2.4 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 investigator's site. Data reported on the Case Report Forms that are derived from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; 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 the source documents:

- Patient identification (initials, gender, data of birth/age)
- Patient participation in the trial (drug, trial number, subject number, date informed consent given)
- Dates of Patient's visits
- Medical history
- Medication history
- AE onset and end
- SAE onset and end
- Originals or copies of laboratory results
- Originals or copies of ultrasound findings or MRI findings or FibroScan® findings and other results if applicable.
- Conclusion of patient's participation in the trial.

9.2.5 Direct Access to Source Data / Documents

The Investigator/ institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, 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 and inspection by health authorities (e.g., FDA, or other applicable regulatory authorities). The on-site monitor will review all eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.2.4.

9.2.6 Trial Monitoring

It is the responsibility of the Investigator 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 Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designees will review with the Investigator 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 Investigator will permit the Sponsor or their designees 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 Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

9.2.7 Query Handling and Error Management

If there are any discrepancies/errors/corrections are needed in the data entered in the eCRF then the responsible monitor or data manager will raise a query in the electronic data capture application. The designee staff at the study site will answer queries sent to the investigator. This process will be continued till the discrepancies/errors are adequately resolved.

9.3 QUALITY CONTROL AND QUALITY ASSURANCE AUDIT

A quality assurance audit of this trial may be conducted by the sponsor or sponsor's designee. The quality assurance auditor will have access to all medical records, the investigator's trial related files and correspondence, and the informed consent form documentation that is relevant to this clinical trial.

9.4 PROCEDURES

9.4.1 Adverse Events

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

9.4.1.1 Definitions

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

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

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

9.4.1.2 Treatment-emergent Adverse Events

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

9.4.1.3 Collection of Adverse Events

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

9.4.1.4 Assessment of Adverse Events

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

Severity

The PI will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. Severity will be assessed according to the following scale:

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

Moderate: Event introduces a low level of inconvenience or concern to the patient and may interfere with daily activities, but is usually improved by simple therapeutic measures. Moderate experiences may cause some interference with functioning.

Severe: Event interrupts the patient's normal daily activities and generally requires systemic drug therapy or other treatment. Severe events are usually incapacitating.

Causality

For all AEs, the PI will provide an assessment of causal relationship to study drug. The causality assessment must be recorded on the appropriate AE reporting page of the patient's 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 by other conditions.
- Probably related: Suggests that a reasonable temporal sequence of the AE with study drug administration exists and, based upon the PI's clinical experience, the association of the AE with study drug seems likely.
- Definitely related: Suggests that a causal relationship exists between the study drug and the AE, and other conditions (concomitant illness, progression or expression of the disease state, reaction to concomitant medication) do not appear to explain the AE.
- Unknown

Outcome

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

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

9.4.1.5 Recording Adverse Events

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

9.4.1.6 Follow-up of Adverse Events

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

9.4.2 Serious Adverse Event

An SAE is an event that:

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

Serious AEs also include events that are medically significant in the PI's judgment, including medically significant laboratory abnormalities, such as those that warrant stopping study drug for individual patients as specified in Section 4.5 of the protocol. In general, medically significant events require medical/surgical intervention to prevent one of the outcomes listed above.

9.4.2.1 Reporting Serious Adverse Events

The PI must report any SAEs to the Sponsor/Contract Research Organization (CRO) within 24 hours of becoming aware of the event.

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

The PI and the Sponsor (or Sponsor's designated personnel) will review each SAE report and the Sponsor/CRO will evaluate the seriousness and the causal relationship of the event to study drug.

In addition, the Sponsor (or Sponsor's designated personnel) will evaluate the expectedness according to the reference document (Investigator Brochure or Summary of Product Characteristics). Based on the PI and Sponsor's assessment of the event, a decision will be made concerning the need for further action. All SAEs will be recorded from signing of informed consent until the end of the study (i.e., the safety telephone call). Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours.

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

1. On discovery, all SAEs should be immediately reported (latest within 24 hours of knowledge of the event) to Sponsor/CRO, complete the SAE report form and fax or email the documents to Sponsor/CRO. Details regarding the safety management will be specified in safety management plan.

9.4.3 Expected Adverse Events

Adverse events reported by 2% or more patients treated with Saroglitazar Magnesium during the double-blind, active-controlled trial with Pioglitazone as the comparator regardless of causality included gastritis and asthenia. In the double-blind placebo controlled study, AEs reported by 2% or more patients treated with Saroglitazar Magnesium included gastritis, dyspepsia, pyrexia and pain. The details of AE experienced during the Saroglitazar Magnesium studies are mentioned in an Investigator Brochure. The investigators will provide instructions and medical management to the patients for the symptoms of potential adverse effects such as skeletal muscle pain, weight gain, peripheral edema and shortness of breath.

9.4.4 Emergency procedures

Any serious or significant AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately to the Sponsor/CRO. Details regarding this reporting procedure will be provided in the safety management plan.

9.4.5 Pregnancy

- At screening every female subject of childbearing potential will be tested for serum pregnancy test. Women are advised not to become pregnant during the trial and for at least 4 weeks ±3 days after the end-of-treatment period. Adequate contraceptive measures

shall be taken to prevent pregnancy. Even when contraceptive methods are used, there is a small risk that pregnancy might occur.

- In case a subject becomes pregnant, then she will be withdrawn from the trial and adequate monitoring of the subjects will be conducted. It is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 4 weeks ±3 days of completing the treatment period.
- Women who become pregnant while on trial drug (and up to 4 weeks ± 3 days following active treatment), an adequate monitoring will be done as follows:
    a. If the woman wants to continue the pregnancy, she will be provided proper obstetrical care.
    b. The investigator should ensure that the subject has access to an obstetrician for the entire duration of her pregnancy and the delivery. The investigator should regularly follow up with the obstetrician regarding the health status of the subject.

If the woman decides to terminate her pregnancy, she will be provided proper gynaecological care. The investigator should ensure that the subject has access to a gynaecologist for the termination of her pregnancy. The investigator should regularly follow up with the gynaecologist regarding the health status of the subject.

9.4.5.1 Outcomes of Pregnancy

- If the pregnancy continues to term, the outcome (health of infant) must also be reported. The investigator should report the pregnancy to Sponsor Clinical Safety within 24 hours of being notified. Sponsor Clinical Safety will then forward the Exposure in Utero form to the investigator for completion.
- Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal anomalies, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious adverse events.

The following information regarding infants delivered at term will be collected and reported:

- Congenital anomalies (will be considered as a serious adverse event) (Any infant with a congenital anomaly should be examined by a dysmorphologist for confirmation of the defect)
- Pre-term births (will be considered as a neonatal adverse event of special interest)
- Intrauterine growth restriction (will be considered as a neonatal adverse event of special interest)
- Large for gestational age infants (will be considered as a neonatal adverse event of special interest)

9.4.5.2 Follow-up of Infants:

All exposed infants will be followed up at the following time points:

- At birth
- 4 weeks of age
- Between six months and one year of age

9.5 RULES FOR AMENDING PROTOCOL

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB, in accordance with local legal requirements. This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC/IRB approval before implementation (if appropriate). Following approval, the protocol amendment(s) will be submitted to the Investigational New Drug under which the study is being conducted.
Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.6 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

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

9.7 STATEMENT OF CONFIDENTIALITY

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

9.8 FINAL REPORT AND PUBLICATION POLICY

A report will be prepared under the responsibility of Investigators and according to the standards of the Sponsor. It will include the tabulated raw data and the biostatistical report on the data.
By signing the clinical study protocol, the Investigator agrees with the use of results of the clinical study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without the sponsor's prior written consent.

9.9 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 trial will be kept as per the applicable regulatory requirements. According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements. No document pertinent to the trial shall be destroyed without prior written agreement between the Sponsor and the Investigator.

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11 APPENDICES

11.1 Appendix 1: List of Known CYP2C8 Inhibitors/Substrates

Selected inducers, inhibitors and substrates of CYP2C8		
Substrates	**Inhibitors**	**Inducers**
• Amodiaquine[a] (antimalarial, anti-inflammatory) • Cerivastatin[a] (statin) • Enzalutamide (antiandrogen) • Paclitaxel[a] (chemotherapeutic) • Repaglinide[a] (antidiabetic) • Torsemide[a] (loop diuretic) • Sorafenib[a] (tyrosine kinase inhibitor) • Rosiglitazone (antidiabetic) - converted to active metabolites[b] • Buprenorphine (semisynthetic opioid) • Polyunsaturated fatty acids • Montelukast (leukotriene receptor antagonist)	**Strong** • Gemfibrozil[a] (hypolipidemic) **Moderate** • Trimethoprim[a] (antibiotic) **Unspecified potency** • Thiazolidinediones[a] (antidiabetic) • Montelukast[a] (leukotriene receptor antagonist) • Quercetin[a] (antiinflammatory)	**Unspecified potency** • Rifampicin[a] (antibiotic)

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

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

11.2 Appendix 2: Declaration of Helsinki

12 PROTOCOL SIGNATURE

STUDY TITLE:

A Phase 2A, Double-blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Saroglitazar Magnesium 4 mg Tablets for Treating Non-alcoholic Fatty Liver Disease (NAFLD) in Women With Polycystic Ovary Syndrome (PCOS).

RESPONSIBILITY	NAME AND DESIGNATION	DATE AND SIGNATURE
STUDY DIRECTOR, SPONSOR MEDICAL EXPERT AND MANAGEMENT APPROVAL	**Dr. Deven V Parmar, MD** Senior Director & Head – Clinical R & D [redacted]	[redacted]

SPONSOR APPROVAL

STUDY TITLE:

A Phase 2A, Double-blind, Randomized, P lacebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Saroglitazar Magnesium 4 mg Tablets for Treating Non-alcoholic-Fatty Liver Disease (NAFLD) in Women With Polycystic Ovary Syndrome (PCOS).

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 (R2) the

DECLARATION OF INVESTIGATOR

STUDY TITLE:

A Phase 2A, Double-blind, Randomized, P lacebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Saroglitazar Magnesium 4 mg Tablets for Treating Non-alcoholic-Fatty Liver Disease (NAFLD) in Women With Polycystic Ovary Syndrome (PCOS).

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 investigators and all other pertinent requirements of the ICH E6 (R2) 'Guidelines on Good Clinical Practice', Declaration of Helsinki and other 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 a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I 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 fo

[redacted]