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CLINICAL TRIAL PROTOCOL

Protocol No.	SARO.16.004
Version No. and Date	6.0, dated 21 August 2019
Superseded Protocol No	SARO.16.004
Version No. and Date	5.0, dated 24 October 2018
Investigational Product(s)	Saroglitazar Magnesium ([redacted])
Title:	A Phase 2, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability and Efficacy of Saroglitazar Magnesium in Patients with Primary Biliary Cholangitis **(EPICS)**
Clinical Phase	Phase 2
Sponsor	Zydus Discovery DMCC Unit No 909, Armada 2 Plot No: JLT-PH2-P2A, Jumeriah Lakes Towers Dubai UAE P.O Box 113536
Study Director: **(Sponsor's Representative)**	Dr. Deven V Parmar, MD [redacted]
Sponsor's Medical Expert and Monitor	[redacted]

Clinical Laboratory	[redacted]
Bio analytical Laboratory for Pharmacokinetic Assessment	[redacted]
Data Management and Biostatistics	[redacted]
Planned Date of Trial	December 2018
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STUDY PROTOCOL SUMMARY

Name of Sponsor	Zydus Discovery DMCC Unit No 909, Armada 2 Plot No: JLT-PH2-P2A, Jumeriah Lakes Towers Dubai UAE P.O Box 113536
Name of the Test Product	Saroglitazar Tablet [redacted]
Name of Active Ingredient of Test Product	Saroglitazar Magnesium 2 mg and 4 mg
Name of the Reference Drug	Placebo tablet
Name of Active Ingredient of Reference Product	Placebo
Potential Indication	Primary Biliary Cholangitis
Study Subjects	Patients with Primary Biliary Cholangitis
Clinical Phase	Phase 2
Trial Number	SARO.16.004
Treatment Duration	16 weeks double-blind treatment
Planned Study Period	20 weeks

Study Title: A Phase 2, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability and Efficacy of Saroglitazar Magnesium in Patients with Primary Biliary Cholangitis

Background:

Primary Biliary Cholangitis (PBC; previously referred to as "Primary Biliary Cirrhosis") is a chronic progressive, autoimmune cholestatic disease that mainly affects middle-aged women. It is characterized by progressive inflammatory destruction of the intrahepatic small and medium-size bile ducts and resulting in bile duct destruction, ductopenia and portal fibrosis that progresses slowly to biliary cirrhosis and subsequent liver failure. Fatigue (65% to 85% of patients) and pruritus (25 – 70% of patients) are the two common symptoms and have a major impact on quality of life (QoL) in patients with PBC. Additionally hyperlipidemia occurs in up to 85% of patients, and could even be the initial serum abnormality in PBC.

The etiology and exact pathogenesis of PBC are still not clear, and proposed to be related to a combination of genetic factors, viral and bacterial infections, autoantibodies to mitochondrial antigens, and/ or environmental factors. At present ursodeoxycholic acid (UDCA) is the first line therapeautic agent and obeticholic acid (OCA) is the second line agent for UDCA intolerant or unresponsive. However, OCA is associated with dose-related worsening in pruritus. In the POISE trial, pruritus occurred more frequently in the OCA-treated groups relative to placebo, with 38%, 56%, and 68% of patients experiencing pruritus in the placebo, 5-10 mg, and 10 mg groups, respectively. Adverse changes in lipid levels, mostly due to reductions in high-density lipoprotein (HDL), were also common in all OCA-treated patients.

It has been reported that patients treated with UDCA monotherapy also have a suboptimal response in endpoints (alkaline phosphatase [ALP], alanine aminotransferase [ALT], or immunoglobulin

[Ig]M), and some of patients will subsequently die or require liver transplantation, thus indicating a clear need for additional therapies.

Ligand-activated peroxisome proliferator-activated receptor alpha (PPARα) contributes to a range of actions including cholesterol and bile acid homeostasis. PPARα primarily downregulates BA synthesis through inhibition of the BA-synthesizing enzymes, cytochrome P450 cholesterol 7A1-hydroxylase (CYP7A1). PPARα is the molecular target of fibrates and improvements in liver enzymes and lipid profiles have been reported with their use. Fenofibrate has been evaluated for cholestatic liver diseases. A recent study reported significantly higher decompensation-free and transplant-free survival in patients treated with fenofibrate and UDCA when compared to UDCA alone.

Saroglitazar, [redacted] it is a potent and predominant PPARα agonist with moderate PPARγ agonistic activity. Saroglitazar magnesium is the first glitazar granted marketing authorization in India and is indicated for treatment of diabetic dyslipidemia and hypertriglyceridemia with type 2 diabetes mellitus not controlled by statin therapy. 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.

There is strong mechanistic rationale for studying Saroglitazar magnesium in PBC due to its α/γ agonist activity. Moreover, Saroglitazar magnesium also improved liver function biomarkers, i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) in patients with nonalcoholic steatohepatitis (NASH). Therefore, this study is designed to evaluate safety, tolerability and efficacy of Saroglitazar magnesium 2 mg and 4 mg in patients with PBC.

Objectives - The purpose of this study is to evaluate the safety, tolerability, and efficacy of Saroglitazar magnesium in patients with PBC.

Primary Objective:

1. To investigate the effect of a 16-week treatment regimen of Saroglitazar magnesium 2 mg and 4 mg on ALP levels in patients with PBC.

Secondary Objectives:

1. To compare the effect of Saroglitazar magnesium (2 mg and 4 mg) and placebo on below mentioned parameters following a 16-week treatment:

    i. Alkaline Phosphatase

    ii. Lipids profile: TG, TC, HDL, LDL, and VLDL

iii. Liver biochemistries: GGT, ALT, AST, bilirubin and albumin.

iv. Serum total bile acids

v. 7α-hydroxy-4-cholesten-3-one (C4) and

vi. Fibroblast growth factor 19 (FGF19)

2. Proportion of patients with ALP improvement.
3. Quality of life (QoL) by using PBC-40.
4. Safety and tolerability of Saroglitazar magnesium 2 mg and 4 mg.
5. Pharmacokinetics of Saroglitazar.

Criteria for Inclusion/Exclusion

Inclusion criteria:

1. Males or females, between 18 and 75 years of age, inclusive.
2. a) Patients on therapeutic doses of Ursodeoxycholic acid (UDCA) for ≥12 months and stable therapy for ≥3 months prior to enrolment

   OR

   b) Patients who are unable to tolerate UDCA, and did not receive UDCA for at least 3 months from the date of screening.
3. History of confirmed Primary Biliary Cholangitis Diagnosis, based on American Association for the Study of Liver Disease [AASLD] and European Association for Study of the Liver [EASL] Practice Guidelines [Lindor 2009; EASL 2009], as demonstrated by the presence of at least ≥2 of the following 3 diagnostic factors:
   - History of elevated ALP levels for at least 6 months at Screening Visit 1
   - Positive antimitochondrial antibodies (AMA) titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex])
   - Liver biopsy consistent with PBC.
4. ALP ≥1.67x upper limit of normal (ULN) at Visit 1 and Visit 2 and with < 30% variance between the levels from Visit 1 to Visit 2.

5. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal, agree to use ≥ 1 effective method of contraception during the trial. Effective methods of contraception are considered to be hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or double barrier method, i.e., (a) condom (male or female) or (b) diaphragm, with spermicide; or Intrauterine device (IUD); or Vasectomy (partner).

6. Must provide written informed consent and agree to comply with the trial protocol.

Exclusion criteria:

1. Consumption of >3 units of alcohol per day (>21 units per week) if male and >2 units of alcohol per day (>14 units per week) if female for at least 3 consecutive months in the last 5 years (Note: 1 unit = 12 ounces of beer, 4 ounces of wine or 1 ounce of spirits/hard liquor).
2. History or presence of other concomitant liver diseases including:
   - Hepatitis B or C virus (HCV, HBV) infection
   - Primary sclerosing cholangitis (PSC)
   - Alcoholic liver disease
   - Definite autoimmune hepatitis (AIH) or overlap syndrome of AIH with PBC
   - Non-alcoholic steatohepatitis (NASH).
3. Cirrhosis with complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin > 2x ULN, ascites, encephalopathy or variceal bleed, known esophageal varices or history of variceal bleeding and active or history of hepatorenal syndrome.
4. History of any venous thromboembolism, TIA, intracranial hemorrhage, neoplasm, arteriovenous malformation, vasculitis, bleeding disorder, coagulation disorders or screening blood tests that indicate altered coagulability (e.g. platelet count, aPTT, PTT or TT tests).
5. Patients with INR > ULN at visit 1.
6. Patients with total bilirubin > ULN at visit 1 that is not due to Gilbert's syndrome.
7. Patients with >30% increase in ALT, total bilirubin, or INR between visit 1 to visit 2, unless both results (visit 1 and visit 2) are within the reference range.
8. Patients with serum creatinine >ULN according to the gender at Visit 1.
9. Patients with abnormal total creatine kinase (CK) OR lipase OR amylase at Visit 1.
10. Unstable cardiovascular disease, including:
    - unstable angina, (i.e., new or worsening symptoms of coronary heart disease within the past 3 months), acute coronary syndrome within the past 6 months, acute

myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III – IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months

- history of (within prior 3 months) or current unstable cardiac dysrhythmias
- uncontrolled hypertension (systolic blood pressure [BP]>160 mmHg and/or diastolic BP >100 mmHg)
- stroke or transient ischemic attack within the prior 6 months

11. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer.
12. Contraindications to Saroglitazar magnesium or has any conditions affecting the ability to evaluate the effects of Saroglitazar magnesium.
13. Known allergy, sensitivity or intolerance to the study drug, comparator or formulation ingredients.
14. Participation in any other clinical study within the previous 3 months of screening.,
15. Illicit substance abuse within the past 6 months.
16. History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study (such as poorly controlled psychiatric disease, HIV, coronary artery disease or active gastrointestinal conditions that might interfere with drug absorption).

Methodology:

This is a Phase 2 prospective, multicenter, randomized, double-blind, placebo-controlled study planned to enroll a total of 36 patients from ~10-12 sites with a diagnosis of PBC who meet the study's inclusion/exlcusion criteria. The study will be conducted over a period of up to 26 weeks and will include a 6-week Screening Phase, a 16-week double-blind Treatment Phase and a safety follow-up visit after 4 weeks. Six patients in each group are planned for pharmacokinetic assessment therefore a total of 18 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.

Screening Phase

- Visit 1 (Day -42): Patient eligibility for participation in the study will be assessed. Medical history will be obtained and physical examination, electrocardiogram (ECG) and laboratory evaluations (including serology, [anti-nuclear antibody, smooth muscle antibody and serum immunoglobulin level G], clinical chemistry, hematology, liver biochemistries, and urinalysis) will be performed. In patients with ANA or SMA antibody positive titers, a liver biopsy must have been performed to rule out autoimmune hepatitis or overlap syndrome. Female patients will undergo a pregnancy test. Serum ALP must be ≥1.67 upper limit of normal (ULN) to

proceed further in the study.

- Visit 2 (Day -14 to -7): Liver biochemistries (ALT, ALP, total bilirubin (TB) and INR will be re-measured approximately 4 weeks from Day -42 to determine eligibility.

  Elevated ALP must be ≥1.67 ULN on 2 occasions in the Screening Phase and is necessary for study entry. If there is an increase of more than 30% in the levels of ALT, total bilirubin or INR at Day (-14) to Day (-7) [Visit 2] as compared to the values on Day (-42) [Visit 1], then such patients will not be eligible for study entry.

  The average of two assessments (Visit 1 and Visit 2) of liver biochemistries and INR will be considered as baseline values for these parameters.

Randomization & Treatment Phase

- **Visit 3:** The Randomization & Treatment Phase will include 6 outpatient visits over a period of 16 weeks, including the randomization visit. Patients will be randomly assigned to receive either Saroglitazar magnesium (2 mg or 4 mg) or placebo orally once daily in addition to their ongoing treatment with UDCA (Patients unable to tolerate UDCA will receive only the investigational medicinal products), starting on Day 1 and contuining for 16 weeks. Efficacy and safety parameters will be assessed during each study visit as per the Schedule Visit Table.

- **Visit 3.1:** Patient will visit study site at 2 weeks after randomization visit for LFTs. The LFTs will be performed at local laboratory.

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

- **End-of-treatment Visit (Visit 7):** An End-of-double-blind treatment will occur at Week 16 and considered as End of Treatment visit. The clinical assessment, reconciliation of study drug, and measurements of efficacy and safety endpoints will be performed as per the study schedule.

- **Safety Follow-up Visit (Visit 8):** A final post-treatment visit will occur 4 weeks (±3 days) after the End-of-treatment Visit for safety monitoring. A clinical examination and safety lab assessment will be performed during this visit.

Patient withdrawal

In the event a patient is withdrawn from the study prematurely for any reason, the End of Treatment Visit procedures should be followed.

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

1. Subject who reports AE and if considered in Investigator's/Medical Expert's opinion

that it is not in the subject's best interest to continue.

2. Any subject found to have entered the study in violation of this protocol.
3. Subject's lack of compliance to the study protocol.
4. Any subject who wishes to withdraw his / her consent for participation in the study.
5. In case a subject becomes pregnant, then she will be withdrawn from the trial.
6. Any subject who requires the use of unacceptable concomitant medications as mentioned in exclusion criteria and restrictions.
7. Termination of study by sponsor, IRB/IEC, or the regulatory authority.

Discontinuation of Subject Investigational Product (IP)

Patients with worsening liver function will not be enrolled in the study. Evidence of worsening liver function will be assessed based on the 2 initial laboratory values used to establish the baseline. Elevations in ALT and/or AST, occurring after the initiation of study drug, that meet the definition of a potential Case of Drug-Induced Liver Injury per below;

1. If patients with abnormal baseline liver indices develop elevations of AST or ALT greater than 2x baseline or total bilirubin greater than 1.5x baseline values while on study, testing shall be repeated within 48 -72 hours.
2. If there are persistent elevations in ALT or AST greater than 2x baseline or TBL greater than 1.5x baseline values, then close observation (testing and physical examination 2-3 times per week) shall be initiated or study drug will be discontinued
    - A decision to discontinue or temporarily interrupt the study drug will 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. Study drug will be discontinued or temporarily interrupted:
        a. When the baseline values were < 2x ULN, discontinue if ALT or AST increases to > 5x baseline,
        b. When the baseline values were ≥ 2x ULN but < 5x ULN, discontinue if ALT or AST increases to >3x baseline,
        c. When the baseline values were ≥ 5x ULN, discontinue if ALT or AST increases to > 2x baseline,
        d. Discontinue if ALT or AST increase > 2x baseline AND the increase is

accompanied by a concomitant TBL increase to >2x baseline OR the INR concomitantly increases by >0.2,

e. In any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

- If a patient lives in a remote area, laboratory testing can be performed locally and the results shall be promptly communicated to the investigator site promptly.
- If patient develops an adverse event of grade 3 that is probably or possibly related to study drug and any patient regardless of attribution to drug who develops a grade 4 or higher Common Terminology Criteria for Adverse Event (CTCAE version 4.03).
- Parameters of renal function: IP is to be discontinued if the estimated glomerular filtration rate (eGFR) falls to <60 mL/min/1.73m^2 (calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) and where the value is reconfirmed after 24 hrs repeat. Additionally, any subject who requires renal replacement therapy will also have IP discontinued.
- Patient will be immediately discontinued from study drug and followed until resolution of adverse event and laboratory values have returned to baseline, if any of the following cerieria occur.
    a. TB ≥3.0 mg/dL in individuals with normal baseline TB. In individuals with elevated baseline TB due to known Gilbert's syndrome, doubling of direct bilirubin will prompt immediate discontinuation of the study drug.
    b. Total CK > 5x ULN
    c. Amylase and lipase > ULN
    d. Hemoglobin < 100 g/L or HCT <30%
    e. Platelets < 100000/µL
    f. WBC <3.5 X 10^9/L
    g. if more than 3 patients develop a CTCAE grade 3 or higher in the same category, or if 3 or more patients meet the above individual criteria (a to f) the trial may be stopped and/ or unblinded safety data will be evaluated

Excluded concomitant medications: Patients are not permitted to take thiazolidinedione (pioglitazone, rosiglitazone), chemotherapy, or other investigational medications during the study. Patients should not take any over-the-counter medications or complementary and/or alternative medications without prior consultation of the Investigator.

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 before study entry. Statins are permitted as concomitant medications; however, patients will be monitored for statin related toxicity when it is co-administered. Glycemic control medications will be permitted as concomitant medications, including antidiabetic drugs such as metformin, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors and insulin. Patients must continue with their current drug regimen without any change in dosage.

Treatment for common illness during the study may be allowed.

Total Enrolment:	A total of 36 patients will be enrolled in a 1:1:1 ratio (12 patients in each arm i.e. Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg and placebo). Six patients in each group are planned for pharmacokinetic assessment therefore a total of 18 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. Additional patients will be enrolled if the dropout rate is more than 20%.
Test Product: **Dose:** **Mode of Administration:**	Saroglitazar magnesium 2 mg and 4 mg Oral (once daily)
Reference Therapy: **Dose:** **Mode of Administration:**	Placebo (provided by sponsor) Matching placebo Oral (once daily)
Duration of Treatment:	16-week double-blind placebo-controlled treatment period

Criteria for Efficacy

Primary Efficacy Endpoint

1. Improvement in ALP levels after 16 weeks of Saroglitazar magnesium 2 mg and 4 mg treatment.

Secondary Efficacy Endpoints

1. To compare the effect of Saroglitazar magnesium (2 mg and 4 mg) and placebo on below mentioned parameters following a 16-week treatment:

    i. Change from baseline in ALP at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to Placebo.

    ii. Change from baseline in lipid profile (TG, TC, HDL, LDL, and VLDL) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to Placebo.

    iii. Change from baseline in liver biochemistries (GGT, ALT, AST, Bilirubin and

albumin) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to Placebo.

iv. Change from baseline in serum total bile acids at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar as compared to Placebo.

v. Change from baseline in 7α-hydroxy-4-cholesten-3-one (C4) at Week 16 in Saroglitazar as compared to Placebo.

vi. Change from baseline in fibroblast growth factor 19 (FGF 19) at Week 16 in Saroglitazar as compared to Placebo.

2. Proportion of patients with ALP improvement, i.e. 15%, 20%, 30%, 40% and normalization at Week 8 and Week 16.

3. Change in QoL at Week 16 by using PBC-40.

4. Change from baseline in ALP in patients who are unable to tolerate UDCA at week 16 in Saroglitazar 2 mg and 4 mg as compared to Placebo.

5. Safety and tolerability of Saroglitazar magnesium 2 mg and 4 mg.

6. Pharmacokinetics of Saroglitazar.

Pharmacokinetics of Saroglitazar will be performed in patients with PBC. The samples will be collected at Pre-dose (0.0), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 24 hours post-dose on Visit 3 and Visit 7. In addition, pre-dose sample will be collected at Visits 4, 5, and 6.

The following pharmacokinetic parameters will be evaluated:

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

xii. Fluctuation index.

Criteria for Safety

- Frequency and severity of adverse events
- Clinical laboratory testing (hematology, clinical chemistry and urinalysis)
- Twelve-lead electrocardiogram (ECG)
- Vital signs
- Body weight and height (at screening)
- Physical examination

Statistical Methods:

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

Demographic characteristics and Baseline Characteristics will be summarized by treatment, subject disposition, reasons for withdrawal or by any other variables as appropriate. Unless otherwise stated, all the continuous variables will be represented by n, mean, standard deviation, minimum, median and maximum. All the categorical variables will be presented as counts and percentages.

Efficacy Analysis:

Modified intent-to-treat (MITT) and Per Protocol (PP) analysis will be carried out for the study trial.

All efficacy analyses will be based primarily on the MITT, and analyses based on the Per Protocol (PP) analysis will be secondary to this.

The MITT population will consist of all patients who have been randomized, taken at least 1 dose of the study treatment and have provided efficacy data for at least 1 post baseline evaluation. Missing values will be imputed by carrying forward the last observation value after baseline.

The PP analysis population will consist of all patients who have completed the treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome.

Primary Efficacy Analysis:

The primary analysis for the primary efficacy endpoint will be based on the MITT. The primary efficacy endpoint in this study is improvement in ALP levels after 16 weeks of Saroglitazar magnesium treatment.

The primary endpoint will be summarized and improvement from baseline to week 16 will be

evaluated using Paired t-Test. Statistical significance will be defined as a p-value <0.05.

Secondary Efficacy Analysis:

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

Endpoints such as change from baseline in ALP at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium groups as compared to placebo; change from baseline in lipid profile (TG, TC, HDL, LDL, and VLDL) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo; change from baseline in liver biochemistries (GGT, ALT, AST, Bilirubin and albumin) at Week 4, Week 8, Week 12 and Week 16 change from baseline in serum total bile acids at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo; change from baseline in C4 and FGF 19 at week 16; and change in QoL (PBC40) at Week 16 will be analyzed using ANCOVA model. Treatment effects will be estimated using the least-square mean, standard error and 95% confidence intervals from ANCOVA model with baseline value as covariate. Comparison will be performed for Saroglitazar magnesium groups (i.e., 2 mg and 4 mg) and placebo using the difference in least-square means from the ANCOVA model. Proportion of patients with ALP improvement, i.e. 15%, 20%, 30%, 40% and normalization at Week 8 and Week 16 will be presented as counts and percentages.

Descriptive statistics will be provided for each pharmacokinetic parameter.

These analyses will also be supported by simple summaries (n, mean, standard deviation, median, minimum and maximum) at each visit.

Safety Analysis:

Safety analyses will be based on the Safety population which will consist of all patients who are known to have received at least 1 dose of study treatment, with patients grouped according to the actual treatment received.

All safety endpoints (AEs, clinical laboratory testing, ECG, 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, and patient counts and percentages for categorical variables.

ABBREVIATIONS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Disease
ADRs	Adverse drug reactions
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibodies
ANA	Anti-nuclear antibody
ANCOVA	Analysis of Co-variance
API	Active pharmaceutical ingredient
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
C4	7α-hydroxy-4-cholesten-3-one
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CAP	College of American Pathologist
CFR	Code of Federal Regulation
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organisation
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	Maximum serum concentration
CSR	Clinical Study Report
CYP	Cytochrome
DPP-4	Dipeptidyl peptidase 4
EASL	European Association for study of the Liver
ECG	Electrocardiogram
ECI	Events of clinical interest
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EDC	Electronic data capture
EPICS	Evaluation in primary biliary cholangitis with Saroglitazar magnesium
FGF 19	Fibroblast growth factor 19
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
HBV	Hepatitis B virus
HCV	Hepatitis C virus

Abbreviation	Definition
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
ICF	Informed consent form
IEC	Independent Ethics Committee
[Ig]M	Immunoglobulin M
IP	Investigational product
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-treat
NASH	Non-alcoholic steatohepatitis
PBC	Primary Biliary Cholangitis
PP	Per-protocol
PPAR	Peroxisome proliferator-activated receptors
PSC	Primary sclerosing cholangitis
QID	Quater in die
QoL	Quality of life
SAE	Serious adverse event
SAS	Statistical Analysis System
SDs	Source documents
SMA	Smooth muscle antibody
SOPs	Standard operating procedures
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TG-C	Triglyceride-cholesterol
TIA	Transient ischemic attack
TT	Thrombin time
TZD	Thiazolidinedione
UDCA	Ursodeoxycholic acid
USFDA	United State of Food and Drug Administration
ULN	Upper limit of normal
VLDL	Very low density lipoprotein
WHO	World Health Organisation
ZYDUS	Zydus Discovery DMCC

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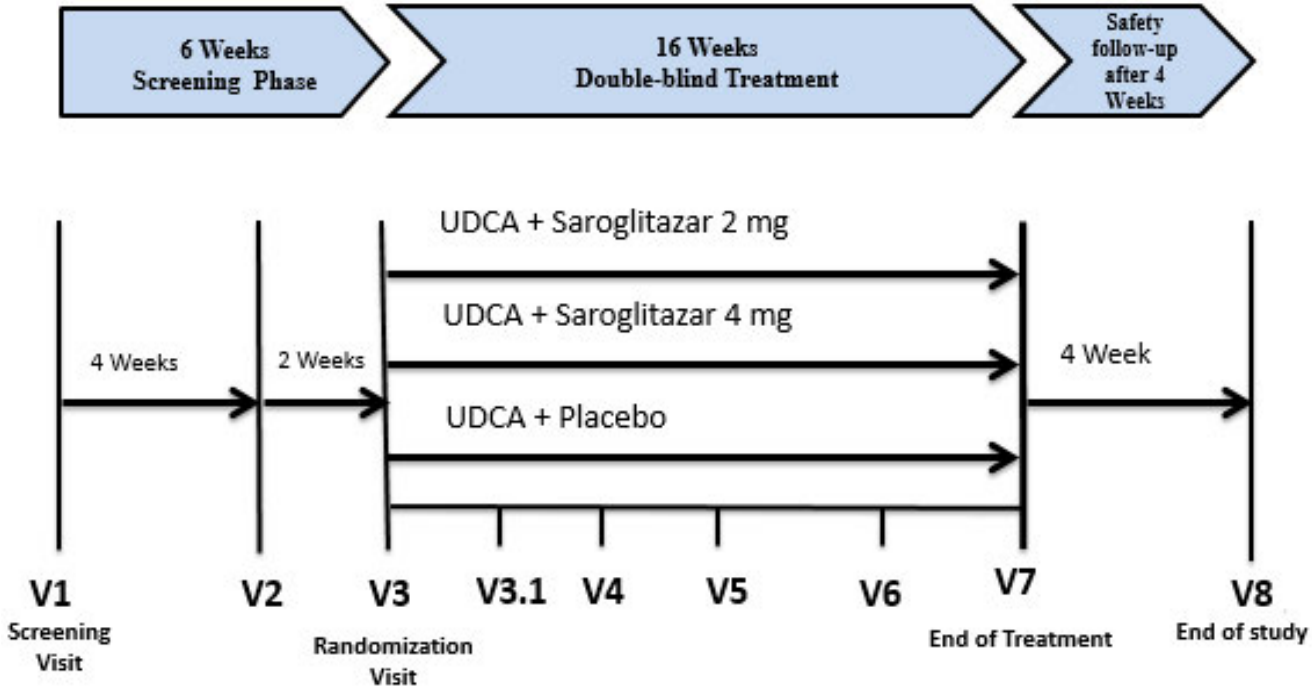

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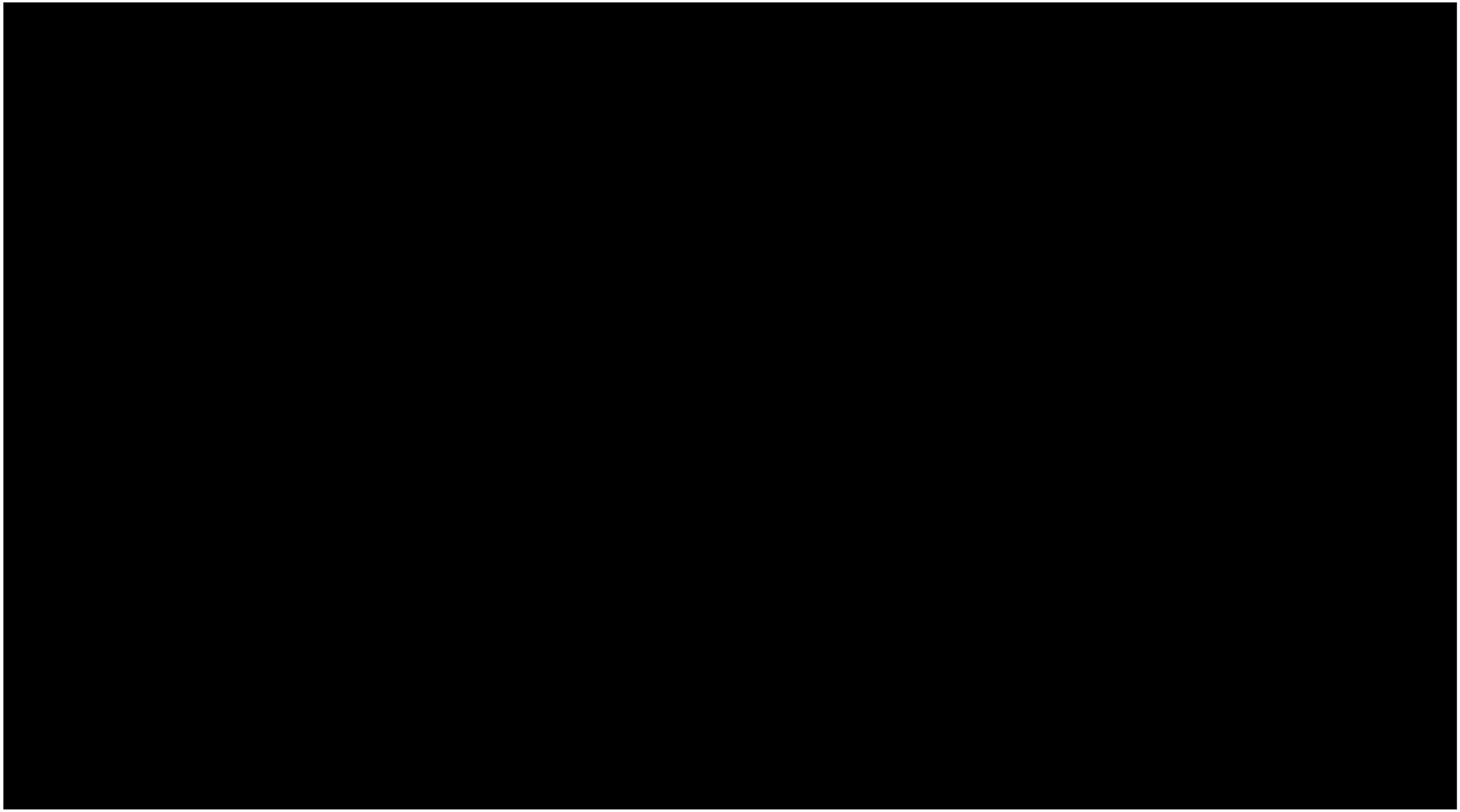

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2 INTRODUCTION

2.1 MEDICAL BACKGROUND

Primary biliary Cholangitis (PBC) previously referred as "Primary biliary cirrhosis (PBC)" is a chronic progressive inflammatory autoimmune mediated cholestatic disease that mainly affects middle age women and is characterized by progressive inflammatory destruction of the interlobular bile duct, and the subsequent development of liver fibrosis and cirrhosis, eventually leading to liver failure (Ulrich et al., 2015; Keith et al., 2009; EASL 2009). Fatigue (65% to 85% of patients) and pruritus (25 – 70% of patients) are the most prevalent symptoms and have a major impact on quality of life (QoL). Additionally Hyperlipidaemia arises in up to 85% of patients, and could be the initial serum abnormality in PBC (Jayant and Keith, 2003).

The etiology and exact pathogenesis of PBC are still not clear, and proposed to be related with genetic factors, viral and bacterial infections, autoimmune status, and environmental factors. At present ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) are approved therapeutic options for the treatment of PBC. But, up to 40% of UDCA-treated patients have an inadequate biochemical response, depending on the criteria used, and such patients have significantly worse transplant-free survival rates than UDCA-responsive patients (Gideon et al., 2015). Recently, OCA has been approved for use in PBC patients who are UDCA unresponsive or intolerant. However, OCA is associated with an increase in pruritus and its tolerability may be sub-optimal in the real world. In the POISE trial, pruritus occurred more frequently in the OCA-treated groups relative to placebo, with 38%, 56%, and 68% of patients experiencing pruritus in the placebo, 5-10 mg, and 10 mg groups, respectively. Adverse changes in lipid levels, mostly due to reductions in high-density lipoprotein (HDL), were also common in all OCA-treated patients. Although, it is unclear if these changes by themselves are of any clinical significance (Nevens etal., 2014), the presence of additional risk factors such as smoking and family history of cardiovascular disease is of concern.

2.2 RATIONALE FOR CONDUCTING THE TRIAL

A growing body of literature supports the notion that nuclear receptors are critically involved in the regulation of hepatic bile salt secretion and bile formation. In particular, PPARα which

is highly expressed in liver, muscle, kidney and heart regulates the transcription of several genes involved in lipid metabolism, cholesterol and bile acid homeostasis through inhibition of cytochrome P450 cholesterol 7A1-hydroxylase (CYP7A1), the rate limiting step in bile acid synthesis.

PPARα is the molecular target for the fibrate hypolipidemic agents, including fenofibrate, gemfibrozil and clofibrate, which are FDA-approved for the treatment of dylipidemia, though each fibrate differs in its specificity for the different PPAR subtypes, α, β/δand γ. Fibrates were first noted to reduce hepatic alkaline phosphatase (ALP) isoenzyme levels during their development as cholesterol-lowering agents in the 1970s (Zumoff 1977). Since then, case reports and pilot studies demonstrated the efficacy of bezafibrate and fenofibrate in reducing the biomarkers of cholestatis and liver test abnormalities (Ghonem et al., 2015). A recent study reported significantly higher decompensation-free and transplant-free survival in patients treated with fenofibrate and UDCA when compared to UDCA alone (Cheung et al., 2016).

Saroglitazar magnesium [redacted]), a dual PPAR agonist with predominantly PPARα and a moderate PPARγ agonist, is approved in India at the doses of 2 mg and 4 mg QD for the treatment of "diabetic dyslipidemia" and "hypertriglyceridemia with type 2 diabetes mellitus (T2DM) not controlled by statin therapy". Saroglitazar magnesium Phase 2 and 3 studies in patients with dyslipidemia with and without diabetes, and in patients with NASH demonstrated potential of favorably modulating the predicting markers of PBC (alkaline phosphate and Gamma-glutamyl transferase) in addition to its anti-hypertriglyceridemia activity.

There is a strong mechanistic rationale for studying PPARα/γ agonist in PBC, therefore, this proof of concept placebo-controlled Phase 2 study is designed to evaluate the Safety, Tolerability and Efficacy of Saroglitazar magnesium (2 mg and 4 mg) in Patients with PBC.

Pre-clinical Experience

[redacted]

[redacted]

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

[redacted]

Clinical Experience

Maximum Tolerated Dose in Phase 1 was 16 mg/day for 10 days was found to be well tolerated. In Phase I trials in healthy human volunteers, Saroglitazar magnesium was found to be well tolerated in single[Jani et al., 2013] and multiple dose studies without any safety concern. Several Phase 2 study 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 and without 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 TG-C, total cholesterol and FPG levels. Saroglitazar magnesium has been tested in Phase 2 for NASH at 4 mg dosage form and demonstrated statistically significant reduction of ALT levels compared to placebo which was measured as the primary endpoint. [redacted]

2.3 DRUG PROFILE

[redacted]

2.4 RISK AND BENEFIT

The safety and tolerability of Saroglitazar magnesium is well-established on the basis of pre-clinical and clinical studies (Phase 1 to Phase 3).This study will evaluate the safety and efficacy of Saroglitazar magnesium in Primary Biliary Cholangitis patients. The commonly reported adverse events (AEs) during clinical studies were gastritis, asthenia and pyrexia.

Saroglitazar magnesium is approved in India at doses of 2 mg and 4 mg QD for the treatment of “diabetic dyslipidemia” and “hypertriglyceridemia with T2DM not controlled by statin therapy”.

3 STUDY OBJECTIVES

The purpose of this study is to evaluate the safety, tolerability and efficacy of Saroglitazar magnesium in patients with Primary Biliary Cholangitis.

3.1 PRIMARY OBJECTIVES

1. To investigate the effect of a 16-week treatment regimen of Saroglitazar magnesium 2 mg and 4 mg on ALP levels in patients with Primary Biliary Cholangitis.

3.2 SECONDARY OBJECTIVES

1. To compare the effect of Saroglitazar magnesium (2 mg and 4 mg) and placebo on below mentioned parameters following a 16-week treatment:
    i. Alkaline Phosphatase
    ii. Lipids profile: TG, TC, HDL, LDL, and VLDL
    iii. Liver biochemistries: GGT, ALT, AST, bilirubin and albumin.
    iv. Serum total bile acids
    v. 7α-hydroxy-4-cholesten-3-one (C4)
    vi. Fibroblast growth factor 19 (FGF19)
2. Proportion of patients with ALP improvement.
3. Quality of life by using (PBC40; Jacoby et al., 2005).
4. Safety and tolerability of Saroglitazar magnesium 2 mg and 4 mg.
5. Pharmacokinetics of Saroglitazar.

3.3 SAFETY ASSESSMENT

To assess the safety of Saroglitazar magnesium in the study population over the duration of study.

- Frequency and severity of adverse events
- Clinical laboratory testing (hematology, clinical chemistry and urinalysis)
- Twelve-lead electrocardiogram (ECG)
- Vital signs

- Body weight and height (at screening)
- The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems.

4 STUDY POPULATION

4.1 NUMBER OF SUBJECTS PLANNED

A total 36 subjects (including 20% dropout), will be enrolled on competitive basis at ~10-12 sites in a ratio of 1:1:1 to have 12 subjects in each arm i.e., Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg and placebo. Six patients in each group are planned for pharmacokinetic assessment therefore a total of 18 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. Additional patients will be enrolled if the dropout rate is more than 20%.

4.2 INCLUSION CRITERIA

1. Males or females, between 18 and 75 years of age, inclusive.
2. a) Patients on therapeutic doses of Ursodeoxycholic acid (UDCA) for ≥12 months and stable therapy for ≥3 months prior to enrolment.

   OR

   b) Patients who are unable to tolerate UDCA, and did not receive UDCA for at least 3 months from the date of screening.
3. History of confirmed Primary Biliary Cholangitis Diagnosis, based on American Association for the Study of Liver Disease [AASLD] and European Association for Study of the Liver [EASL] Practice Guidelines; [Lindor 2009; EASL 2009], as demonstrated by the presence of at least≥2 of the following 3 diagnostic factors:
   - History of elevated Alkaline Phosphatase levels for at least 6 months prior to Screening Visit 1
   - Positive antimitochondrial antibodies (AMA) titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex])
   - Liver biopsy consistent with PBC.

4. ALP ≥1.67x upper limit of normal (ULN) at Visit 1 and Visit 2 and with < 30% variance between the levels from Visit 1 to Visit 2.
5. Contraception: Female patients must be postmenopausal, surgically sterile, or if premenopausal, agree to use ≥ 1 effective method of contraception during the trial. Effective methods of contraception are considered to be Hormonal (e.g., contraceptive pill, patch, intramuscular implant or injection); or Double barrier method, i.e., (a) condom (male or female) or (b) diaphragm, with spermicide; or Intrauterine device (IUD); or Vasectomy (partner).
6. Must provide written informed consent and agree to comply with the trial protocol.

4.3 EXCLUSION CRITERIA

1. Consumption of >3 units of alcohol per day (>21 units per week) if male and >2 units of alcohol per day (>14 units per week) if female for at least 3 consecutive months in the last 5 years (Note: 1 unit = 12 ounces of beer, 4 ounces of wine or 1 ounce of spirits/hard liquor).
2. History or presence of other concomitant liver diseases including:
   - Hepatitis B or C virus (HCV, HBV) infection
   - Primary sclerosing cholangitis (PSC)
   - Alcoholic liver disease
   - Definite autoimmune liver disease or overlap syndrome
   - Non-alcoholic steatohepatitis (NASH)
3. Cirrhosis with complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin > 2x ULN, ascites, encephalopathy, known esophageal varices or history of variceal bleeding and active or history of hepatorenal syndrome.
4. History of any venous thromboembolism, TIA, intracranial hemorrhage, neoplasm, arteriovenous malformation, vasculitis, bleeding disorder, coagulation disorders or screening blood tests that indicate altered coagulability (e.g. platelet count, aPTT, PTT or TT tests).
5. Patients with INR > ULN at visit 1.

6. Patients with total bilirubin > ULN at visit 1 that is not due to Gilbert's syndrome.
7. Patients with >30% increase in ALT, total bilirubin, or INR between Visit 1 to Visit 2, unless both results (visit 1 and visit 2) are within the reference range.
8. Patients with serum creatinine >ULN according to the gender at Visit 1.
9. Patients with abnormal total creatine kinase (CK) OR lipase OR amylase at Visit 1.
10. Unstable cardiovascular disease, including:
    - unstable angina, (i.e., new or worsening symptoms of coronary heart disease within the past 3 months), acute coronary syndrome within the past 6 months, acute myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III – IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months
    - history of (within prior 3 months) or current unstable cardiac dysrhythmias
    - uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg and/or diastolic BP >100 mmHg)
    - stroke or transient ischemic attack within the prior 6 months
11. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer.
12. Contraindications to Saroglitazar magnesium or has any conditions affecting the ability to evaluate the effects of Saroglitazar magnesium.
13. Known allergy, sensitivity or intolerance to the study drug, comparator or formulation ingredients.
14. Participation in any other clinical study within the previous 3 months of screening.
15. Illicit substance abuse within the past 6 months.
16. History or other evidence of severe illness or any other conditions that would make the patient, in the opinion of the investigator, unsuitable for the study (such as poorly controlled psychiatric disease, human immunodeficiency virus (HIV), coronary artery disease or active gastrointestinal conditions that might interfere with drug absorption).

4.4 WITHDRAWAL CRITERIA

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

1. Subject who reports AE and if considered in Investigator's/Medical Expert's opinion that it is not in the subject's best interest to continue.
2. Any subject found to have entered the study in violation of this protocol.
3. Subject's lack of compliance to the study protocol.
4. Any subject who wishes to withdraw his / her consent for participation in the study.
5. In case a subject becomes pregnant, then she will be withdrawn from the trial.
6. Any subject who requires the use of unacceptable concomitant medications as mentioned in exclusion criteria (Section 4.3) and restrictions (Section 5.10).
7. Termination of study by sponsor, IRB/IEC, or the regulatory authority.

4.4.1 Discontinuation of Subject Investigational Product (IP)

Patients with worsening liver function will not be enrolled in the study. Evidence of worsening liver function will be assessed based on the 2 initial laboratory values used to establish the baseline.

Elevations in ALT and/or AST, occurring after the initiation of study drug, that meet the definition of a potential Case of Drug-Induced Liver Injury per below;

1. If patients with abnormal baseline liver indices develop elevations of AST or ALT greater than 2x baseline or total bilirubin greater than 1.5x baseline values while on study, testing shall be repeated within 48 -72 hours.
2. If there are persistent elevations in ALT or AST greater than 2x baseline or TBL greater than 1.5x baseline values, then close observation (testing and physical examination 2-3 times per week) shall be initiated or study drug will be discontinued

- A decision to discontinue or temporarily interrupt the study drug will 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. Study drug will be discontinued or temporarily interrupted:

a. When the baseline values were < 2x ULN, discontinue if ALT or AST increases to > 5x baseline,
b. When the baseline values were ≥ 2x ULN but < 5x ULN, discontinue if ALT or AST increases to >3x baseline,
c. When the baseline values were ≥ 5x ULN, discontinue if ALT or AST increases to > 2x baseline,
d. Discontinue if ALT or AST increase > 2x baseline AND the increase is accompanied by a concomitant TBL increase to >2x baseline OR the INR concomitantly increases by >0.2,
e. In any patients with signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

- If a patient lives in a remote area, laboratory testing can be performed locally and the results shall be promptly communicated to the investigator site promptly.
- If patient develops an adverse event of grade 3 that is probably or possibly related to study drug and any patient regardless of attribution to drug who develops a grade 4 or higher Common Terminology Criteria for Adverse Event (CTCAE version 4.03).
- Parameters of renal function: IP is to be discontinued if the estimated glomerular filtration rate (eGFR) falls to <60 mL/min/1.73m^2 (calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) and where the value is reconfirmed after 24 hrs repeat. Additionally, any subject who requires renal replacement therapy will also have IP discontinued.
- Patient will be immediately discontinued from study drug and followed until resolution of adverse event and laboratory values have returned to baseline, if any of the following criteria occur.

a. TB ≥3.0 mg/dL in individuals with normal baseline TB. In individuals with elevated baseline TB due to known Gilbert's syndrome, doubling of direct bilirubin will prompt immediate discontinuation of the study drug.
b. Total CK > 5x ULN
c. Amylase and lipase > ULN
d. Hemoglobin < 100 g/L or HCT <30%
e. Platelets < 100000/µL
f. WBC <3.5 X 10^9/L
g. If more than 3 patients develop a CTCAE grade 3 or higher in the same category, or if 3 or more patients meet the above individual criteria (a to f) the trial may be stopped and/or unblended safety data will be evaluated.

4.5 HANDLING OF PATIENT WITHDRAWAL

In case of withdrawal of consent, and unless otherwise stated by the patient in the informed consent form, Investigators will be encouraged to get information from the medical care provider, in order to follow the medical status of the patients (especially in cases where the patients have withdrawn their consent after having experienced an adverse event). Investigators will also be expected to try as much as possible to re-contact those patients at the end of the trial, in order to obtain status.

If subject discontinues from the study for any reason, before the End of Treatment Visit, the investigator will make all attempts to carry out all End of treatment Visit procedures.

5 STUDY TREATMENTS / IP MANAGEMENT

Saroglitazar magnesium 2 mg or Saroglitazar magnesium 4 mg or placebo tablet will be administered in patients with Primary Biliary Cholangitis once daily in the morning before breakfast without food, for a period of 16 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**.**

Table 2 Identity of Study Drugs

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

Data source: Investigator's Brochure

[redacted]

5.1.2 Comparator Drug Description

Placebo will be used as comparator, which will be formulated as tablets, and will contain above mentioned excipients in section No. 5.1.1. The IP will be manufactured following current-Good Manufacturing Practice (cGMP) guideline.

5.2 DOSAGE AND TREATMENT SCHEDULE

Patients will receive either Saroglitazar magnesium 2 mg or Saroglitazar magnesium 4 mg or placebo orally once each morning before breakfast without food (as determined by the patient's schedule) for 16 weeks during the double-blind treatment period. However, during

scheduled visits patients will have the IP administered on site after the blood sample collection.

5.3 PACKAGING, LABELLING AND RE-SUPPLY

Tablets of Saroglitazar magnesium (2 mg and 4 mg) and placebo will be packed, labeled and supplied by the Sponsor according to all local legal requirements. [redacted]

All drug supplies must be stored in a temperature-controlled environment for ambient temperature 20-25^{0}C.

All Investigators will be provided with a sufficient number of units of the IP for the conduct of the study. Investigational product would then be dispensed to each subject in such a way that the subject can take the doses in accordance with the protocol. A drug accountability log for recording the receipt, storage, dispensing and return of the IP will be maintained by the Investigator or any designated personnel.

Site will contact the sponsor/designee for re-supply of the Investigational product.

After the study has been completed, the PI must account for all study drug used, unused and partially used. All study drugs will be destroyed at the site (per site's SOPs) or returned to the Sponsor (or designee). Unused drug supplies will be destroyed at the site after approval

for the same by the Sponsor. No study drug will be destroyed or returned until drug accountability has been performed by the study monitor.

5.4 STORAGE CONDITIONS

Investigational product will be stored at room temperature (20°C to 25°C) 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 the study-specific temperature log, and sent to the Sponsor. If the excursion is within 15-30°C, quarantine is not required, and the IP is acceptable for use. If the excursion is outside of the 15-30°C range, the IP must be quarantined until a decision on the stability of the IP is made by the Sponsor. If the excursion goes beyond the range of 15-30^0 C it will be considered as a protocol deviation. All IP supplies in the study will be stored in a secure place with access limited to the Site Pharmacist or the Investigator designated site staff.

5.5 BLINDING / UNBLINDING

The study is a double blind study, hence study participants and investigator will not be made aware which preparation (Saroglitazar magnesium 2 mg or Saroglitazar magnesium 4 mg or placebo), is to be administered. The randmization code will be available to the Investigator, for emergency purposes only. The randomization code will be available on each kit which is concealed in the form of scratchcard. In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator should make every effort to first contact the Sponsor/ designee.

The formulation of Saroglitazar magnesium (2 mg and 4 mg) and placebo IPs will be similar in appearance to make any difference in treatment unobvious to the patients and to maintain adequate blinding of evaluators. Neither the Investigator nor the patient should be able to identify the received treatment.

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator should make every effort to first contact the Sponsor/ designee.

Prior to unblinding the patient's treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the

blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate electronic Case Report Form (eCRF) and source documents.

5.6 METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients will be randomly assigned in 1:1:1 ratio to Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg and placebo. The block randomization schedule will be generated using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA). Each block will contain investigational medicinal products; Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg and placebo. Each block will contain at least 3 kits of IMP for 3 patients i.e., 1 kit of Saroglitazar magnesium 2 mg, 1 kit of Saroglitazar magnesium 4 mg and 1 kits of placebo.

The subject identification number will be established at the site based on the randomization number/kit number/patient number and will be used to identify the subject throughout the study and will be entered on all documentation. The same subject number will not be assigned to more than 1 subject. If a subject is not eligible to receive treatment, or if a subject discontinues from the study, the same subject number cannot be assigned to another subject.

The subjects will first be screened into the study. Once patients are determined to be eligible, they will be randomized. The subject will also be assigned a study drug in accordance to their assigned treatment group upon completion of the randomization.

Patients will be considered randomized as soon as the first allocation of treatment number is assigned. The first study drug intake should take place as soon as possible after randomization (on the same day), under medical supervision.

5.7 SELECTION OF DOSES

Saroglitazar magnesium 2 mg and 4 mg have favorably modified the lipid profile in the dyslipidemic patients during its development in Phase 2 and 3 studies. Based on the efficacy, safety and tolerability results of Saroglitazar magnesium, it is approved in India at the doses of 2 mg and 4 mg QD for the treatment of “Diabetic Dyslipidemia” and “Hypertriglyceridemia with T2DM not controlled by statin therapy”. Saroglitazar

magnesium 2 mg and 4 mg also demonstrated the favorable effects on ALP and GGT. Hence Saroglitazar magnesium 2 mg and 4 mg doses have 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 electronic case report form (eCRF). The site may rely on subject report 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.

i. Statins are permitted as concomitant medications; however, patients will be monitored for statin related toxicity when it is co-administered.
ii. Glycemic control medications will be permitted as concomitant medications, including antidiabetic drugs such as metformin, sulfonylureas, dipeptidyl peptidase 4 (DPP-4) inhibitors and insulin.
iii. Treatment for common illness during the study may be allowed.
iv. 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.

5.9 RESCUE MEDICATION AND ADDITIONAL TREATMENT(S)

The Investigator at his/her discretion will be allowed to offer a rescue medication for clinically significant conditions correlated with the laboratory findings, if required, however, such interventions shall be recorded in the eCRF with description of type of intervention, dose and duration. If medication given is in violation to the protocol, then such subjects will be withdrawn from the trial.

Subjects on antidiabetic drug shall also be assessed on scheduled visits for hyperglycemia/hypoglecemia and rescue medication will also be allowed if required. Treatment for such conditions should be initiated as soon as the need for treatment is identified, 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 should be recorded on the appropriate case report form (CRF).

Investigator's shall advise subjects to report at the site for any inconvenience during the course of trial.

5.10 RESTRICTIONS

Patients are not permitted to take thiazolidinedione (pioglitazone, rosiglitazone), chemotherapy, or other investigational medications during the study duration.

Patients also should not take any over-the-counter medications or complementary and/or alternative medications without prior consultation of the Investigator.

The PI should be alerted if, during the course of the study, a patient requires a new medicine or therapy or a changes to an established dosing regimen.

5.11 OVER DOSE AND DRUG INTERACTION

[redacted]

[redacted]

5.12 TREATMENT COMPLIANCE

The subjects will be asked to bring the container of the study medication on the next follow-up visit; compliance for dosing will be assessed by examination of the container and tablet count by study personnel and documentation on individual drug accountability logs.

6 OBSERVATIONS

6.1 EFFICACY

6.1.1 Primary Endpoint

1. Improvement in ALP levels after 16 weeks of Saroglitazar magnesium 2 mg and 4 mg treatment.

6.1.2 Secondary Endpoints

1. To compare the effect of Saroglitazar magnesium (2 mg and 4 mg) and placebo on below mentioned parameters following a 16-week treatment:
    i. Change from baseline in ALP at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.
    ii. Change from baseline in lipid profile (TG, TC, HDL, LDL, and VLDL) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.
    iii. Change from baseline in liver biochemistries (GGT, ALT, AST, Bilirubin and albumin) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.
    iv. Change from baseline in serum total bile acids, at Week 4, Week 8, Week 12 and Week 16 in saroglitazar as compared to Placebo.
    v. Change from baseline in 7α-hydroxy-4-cholesten-3-one (C4) at Week 16 in saroglitazar as compared to Placebo.
    vi. Change from baseline in fibroblast growth factor 19 (FGF 19) at Week 16 in saroglitazar as compared to Placebo.
2. Proportion of patients with ALP improvement, i.e. 15%, 20%, 30%, 40% and normalization at Week 8 and Week 16.
3. Change in QoL at Week 16 by using PBC40.
4. Change from baseline in ALP in patients who are unable to tolerate UDCA at week 16 in Saroglitazar 2 mg and 4 mg as compared to Placebo.
5. Safety and tolerability of Saroglitazar magnesium 2 mg and 4 mg.
6. Pharmacokinetics of Saroglitazar.

Pharmacokinetics of Saroglitazar Magnesium will be performed in patients with PBC. The samples will be collected at Pre-dose (0.0), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0 and 24 hours post-dose on Visit 3 and Visit 7. In addition, pre-dose sample will be collected at Visits 4, 5, and 6.

The following pharmacokinetic parameters will be evaluated:

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

6.2 SAFETY

To assess the safety of Saroglitazar magnesium in the study population over the duration of study.

- Adverse event(s): frequency and severity of AE / SAEs, drop-out 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:
    - Causality
    - Severity
    - Seriousness
    - Expectedness
- Clinical laboratory testing (hematology, clinical chemistry and urinalysis)

- Twelve-lead electrocardiogram (ECG)
- Vital signs
- Body weight and height (at screening)
- The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems.

All AEs will be captured and notification sent to the Sponsor. All AEs will be captured in eCRF. At a minimum, SAEs will be reported in the CRFs as per the timelines defined in the Protocol in adverse event section. However, each research institution's IRB/IEC reporting requirements may contain shorter timelines.

Serious adverse events reporting must comply with the United State of Food and Drug Administration (USFDA) reporting requirements and IRB/IEC reporting requirements.

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

All biological samples will be assayed by a Sponsor-identified CAP and/or CLIA-certified laboratory, using analytical methods in compliance with standard and validated methodologies, with adherence to written standard operating procedures (SOPs).

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

6.2.1 Appropriateness of Measurement

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

6.2.2 Abnormal Laboratory Findings

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

If the 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.

7 INVESTIGATIONAL PLAN

7.1 STUDY DESIGN AND PLAN

This is a Phase 2 prospective, multicentre, randomized, double-blind, placebo-controlled study includes a total 36 patients with a diagnosis of Primary Biliary Cholangitis. The study will be conducted over a period of up to 26 weeks and will include a 6-week Screening Phase, a 16-week Treatment Phase and a safety follow-up visit after 4 weeks.

Screening Phase:

- Visit 1 (Day -42): Patient eligibility for participation in the study will be assessed. Medical history will be obtained and physical examination, electrocardiogram (ECG) and laboratory evaluations (including serology, [anti-nuclear antibody, smooth muscle antibody and serum immunoglobulin level G], clinical chemistry, hematology, liver biochemistries, and urinalysis) will be performed. In patients with ANA or SMA antibody positive titers, a liver biopsy must have been performed to rule out autoimmune hepatitis or overlap syndrome. Female patients will undergo a pregnancy test. Serum ALP must be ≥1.67 upper limit of normal (ULN) to proceed further in the study.
- Visit 2 (Day -14 to -7): Liver biochemistries (ALT, ALP, total bilirubin (TB) and INR will be re-measured approximately 4 weeks from Day -42 to determine eligibility.

  Elevated ALP must be ≥1.67 ULN on 2 occasions in the Screening Phase and is necessary for study entry. If there is an increase of more than 30% in the levels of ALT, total bilirubin or INR at Day (-14) to Day (-7) [Visit 2] as compared to the values on Day (-42) [Visit 1], then such patients will not be eligible for study entry.

  The average of two assessments (Visit 1 and Visit 2) of liver biochemistries and INR will be considered as baseline values for these parameters.

Randomization & Treatment Phase:

- Visit 3: The Randomization & Treatment Phase will include 6 outpatient visits over a period of 16 weeks, including the randomization visit. Patients will be randomly assigned to receive either Saroglitazar magnesium (2 mg or 4 mg) or placebo orally

once daily in addition to their ongoing treatment with UDCA (Patients unable to tolerate UDCA will receive only the investigational medicinal products), starting on Day 1 and continuing for 16 weeks. Efficacy and safety parameters will be assessed during each study visit as per the Schedule Visit Table 1.

- Visit 3.1: Patient will visit study site at 2 weeks after randomization visit for LFTs. The LFTs will be performed at local laboratory.
- Visits 4, 5 and 6: Patients will visit the study site at Week 4 (Visit 4), Week 8 (Visit 5) and Week 12 (Visit 6) for clinical assessment, dispensation and/or reconciliation of study drug, and measurements of efficacy endpoints.
- End-of-Treatment Visit (Visit 7): An End-of-double-blind treatment will occur at Week 16. The clinical assessment, reconciliation of study drug, and measurements of efficacy and safety endpoints will be performed as per the schedule.

Safety follow-up visit (Visit 8) will occur 4 weeks (± 3 days) after the End-of-treatment Visit for safety monitoring. Clinical examination and safety lab assessment will be performed during this visit.

7.2 STUDY PROCEDURES AT EACH VISIT

Study schedule for the trial is given in Table 1.

- **Screening Visit (Week -6)**

All subjects will be required to sign the informed consent forms (ICF) after understanding the ICF before any trial related procedure is initiated as per the applicable regulatory guideline.

Informed consent process will be documented in source document, ICF and other relevant logs, and signed with dated by the Investigator or designee. Prior to subject participation in the trial, written informed consent will be obtained from each subject (or the subject's legally accepted representative) according to the regulatory and legal requirements of the participating state and country.

Subjects with the history of PBC will be screened for eligibility to participate in the study. Demographic detail, medical history will be recorded. ECG will be performed. Pregnancy test will be performed for women of childbearing potential.

Vital signs, height and weight measurements, and physical and laboratory examinations listed in Table 1 will be carried out in subjects suffering from PBC; those satisfying the inclusion-exclusion criteria will be invited to participate in this study. (The physical examination will consist of an evaluation of the head, neck, eyes, ears, nose, throat, chest, heart, lungs, abdomen, skin, extremities, and the neurological and musculoskeletal systems). Concomitant medications will be recorded. Serum ALP must be ≥1.67 upper limit of normal (ULN) to proceed further in the study.

Visit 2 (Week -2 to -1): Liver biochemistries (ALT, ALP, total bilirubin (TB) and INR will be re-measured approximately 4 weeks from Day -42 to determine eligibility. Physical examination, vital signs and lab investigation will be performed as per Table 1.

Elevated ALP must be ≥1.67 ULN on 2 occasions in the Screening Phase and is necessary for study entry. If there is an increase of more than 30% in the levels of ALT, Total bilirubin or INR at Day(-14) to Day(-7)[Visit 2] as compared to the values on Day (-42)[Visit 1], then such patients will not be eligible for study entry.

The average of two assessments (Visit 1 and Visit 2) of liver biochemistries and INR will be considered as baseline values for these parameters.

- **<u>Visit 3: Randomization Visit (Week 0±3 days)</u>**

After screening, the eligible patients will be randomly assigned to one of the following treatment groups in addition to their ongoing treatment with UDCA (Patients unable to tolerate UDCA will receive only the investigational medicinal products) i.e., Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg, or placebo. Vital signs measurements, weight measurements, physical examination, and laboratory examination will be performed as mentioned in Table 1. Concomitant medications will be recorded. AEs will be noted, if any. Urine pregnancy test will be performed for women of childbearing potential. Subjects will undergo cardiac evaluation (ECG). A 4-week supply of study medication (one bottle) will be dispensed. Baseline quality of life assessment will be performed.

- **Visit 3.1 (Week 2±3 Days)**

Patient will visit study site at 2 weeks after randomization visit for LFTs. The LFTs will be performed at local laboratory.

- **Visit 4 (Week 4±3 Days), Visit 5 (Week 8±3 Days) and Visit 6 (Week 12±3 Days)**

Subjects will be undergo a physical examination and laboratory parameters (safety and efficacy) will be assessed as per Table 1. Vitals signs, body weight will be recorded.
AEs, if any, will be noted. Urine pregnancy test will be performed for women of childbearing potential. Concomitant medications will be recorded. Medication compliance will be checked. Medication will be dispensed on each visit for next 4 weeks.

- **End-of-treatment Visit 7 (Week 16±3 Days)**

Subjects undergo physical examination and laboratory parameters (safety andefficacy) will be assessed as per Table 1. Vitals signs and weight will be recorded. AEs will be noted, if any. Subjects will undergo cardiac (ECG) evaluation. Pregnancy test will be performed for all women of childbearing potential. Concomitant medications will be recorded. Medication compliance will be checked.

- **Safety follow-up Visit 8 End of Study (Week 20±3 Days)**

A safety follow-up visit will be performed 4 weeks after End-of-treatment Visit. Patients clinical examination and safety lab assessment will be performed as per Table 1.

Unscheduled visits- will be allowed any time during the study for assessment and management of AEs and any concurrent clinical conditions. Unscheduled visits shall be captured in the CRF.

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

- During this 16-week program, if it is necessary to follow-up on any AE, a designated person from the center will interview the subject for his/her general health, telephonically.

If subject discontinues the study, due to any reason, before End of Treatment Visit, all procedures of End of Treatment Visit should be carried out.

7.3 PHARMACOKINETIC ASESSMENT

Eighteen subjects will participate in a pharmacokinetic sub-study. 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.

On Study Visit 3, and Study Visit 7 subjects will be asked to remain at the clinic for 10 hours. On these dates, additional blood samples will be collected at the following time-points: pre-dose (0.0), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 10.0. 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 and Visit 7. In addition to these collections, pre dose blood samples will be collected at Study Visits 4, 5, and 6.

The pharmacokinetic blood samples will be sent to a central laboratory as assigned by the sponsor. The total amount of blood drawn for Pharmacokinetic study from each patient over the study will be less than ~120 mL/25tablespoons. A detail pharmacokinetic study plan will be prepared separately.

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 DEVIATIONS

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 necessarily influence

the results/outcome of primary endpoints or subject safety. 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 results/outcome of primary endpoints or subject safety. 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, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution. In all case 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 deviation/violation on separate section. The result will be analysed for all participants with major protocol deviations.

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

7.6 DATA MONITORING COMMITTEE

Safety data including adverse events and liver-related events (i.e., clinically meaningful elevations in liver biochemistries ALT, AST, and bilirubin) will be reviewed regularly by a Data Monitoring Committee. The Data Monitoring Committee will have a formal structure and will operate according to a previously agreed upon remit.

8 BIOSTATISTICS

8.1 STATISTICAL DESIGN

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

8.2 NULL AND ALTERNATIVE HYPOTHESIS

Below is the hypothesis of primary efficacy endpoint:

Null hypothesis: H_0: $\mu_s = 0$

Alternative hypothesis H_1: $-\mu_s > 0$

Where: μ_s = change from baseline in ALP levels of the Saroglitazar magnesium (2 mg and 4 mg).

Rejection of the null hypothesis will lead to conclude that the change from baseline in Saroglitazar magnesium 2 mg and 4 mg is statistically significant and hence the test drug is effective.

8.3 STUDY POPULATION AND PLANNED ANALYSIS

8.3.1 Populations

8.3.1.1 Safety population

The safety population includes the subjects who satisfy all inclusion/exclusion criteria, are randomized and received at least single dose of study medication.

8.3.1.2 Modified intent-to-treat population

The modified intent-to-treat (MITT) population includes: all randomized subjects who received any study drug and have at least one post-randomized efficacy measurement.

All primary and secondary objectives will be analysed using MITT population with LOCF method. Last observation carried forward (LOCF) method will be used as an imputation method for the efficacy variables for MITT analysis.

8.3.1.3 Per-protocol population (PP)

The per-protocol population (PP) includes all randomized patients who meet all the inclusions/exclusion criteria, completed the treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome.

8.3.2 Planned Analysis

Modified intent-to-treat (MITT) and Per Protocol (PP) analysis will be carried out for the efficacy analysis.

All efficacy analyses will be based primarily on the MITT, and analyses based on the Per Protocol (PP) analysis set will be secondary to this.

The MITT will consist of all patients who have been randomized, taken at least 1 dose of the study treatment and have provided at least a post-randomized efficacy data. Missing values will be imputed by carrying forward the last observation value after baseline.

8.3.2.1 Primary Efficacy Analysis

The primary analysis for the primary efficacy endpoint will be based on the MITT. The primary efficacy endpoint in this study is improvement in ALP levels after 16 weeks in Saroglitazar magnesium treatment.
The primary endpoint will be summarized and improvement from baseline to week 16 will be evaluated using Paired t-Test. Statistical significance will be defined as a p-value <0.05.

8.3.2.2 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:

- Change from baseline in ALP at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.

- Change from baseline in lipid profile (TG, TC, HDL, LDL, and VLDL) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.
- Change from baseline in liver biochemistries (GGT, ALT, AST, bilirubin and albumin) at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.
- Change from baseline in serum total bile acids at Week 4, Week 8, Week 12 and Week 16 in Saroglitazar magnesium as compared to placebo.
- Change from baseline in 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF 19) at Week 16 in Saroglitazar magnesium as compared to placebo.
- Proportion of patients with ALP improvement, i.e. 15%, 20%, 30%, 40% and normalization at Week 8 and Week 16.
- Change in QoL at Week 16 by using PBC40.
    - This instrument consists of 6 domain and 40 questions: symptoms, itch, cognition, emotion and social.
- Change from baseline in ALP in patients who are unable to tolerate UDCA at week 16 in Saroglitazar 2 mg and 4 mg as compared to Placebo.
- Pharmacokinetics of Saroglitazar.

The change from baseline will be determined as:

Change = (Post-baseline – Baseline)

Percent Change = (Post-baseline – Baseline) / Baseline * 100

Treatment effects will be estimated using the least-square mean, standard error and 95% confidence intervals from ANCOVA model with baseline value as covariate. Comparison will be done for Saroglitazar magnesium (2 mg and 4 mg) and placebo using the difference in least-square means from the ANCOVA model. Proportion of patients with ALP

improvement, i.e., 15%, 20%, 30%, 40% and normalization at Week 8 and Week 16 will be presented as counts and percentages.

Descriptive statistics will be provided for each pharmacokinetic parameter.

The following pharmacokinetic parameters will be evaluated:

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

Above analyses will also be supported by simple summaries (n, mean, standard deviation, median, minimum and maximum) at each visit.

8.3.3 Safety Analysis

All safety analysis will be carried out on 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, ECG, physical examination and vital signs will be presented for each treatment by visit.

All AEs seen during the study period will be listed. Incidence of all AEs reported during the study will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) (version 19 or higher) by treatment group, body system, frequency, severity, seriousness, and relationship to study drug and expectedness.

8.3.4 Baseline Characteristics

Demographic characteristics and Baseline Characteristics will be summarized by treatment, subject disposition, reasons for withdrawal or by any other variables as appropriate. Unless otherwise stated, all the continuous variables will be represented by n, mean, standard deviation, minimum, median and maximum. All the categorical variables will be presented as counts and percentages.

8.3.5 Interim Analysis

8.3.6 An interim analysis will be conducted when approximately 24th active randomized subject completes the study, that is Week 20 visit assessment. The purpose of this interim analysis is to assess the effect of Saroglitazar Magnesium in PBC patients and to choose the optimal dose for planning the phase III study. The interim analysis will be performed with unmasking of specified individuals from the Sponsor who are not involved in the direct conduct of the trial. The study will continue until all planned subjects complete the study. Treatment masking of individual subjects will remain intact for all subjects, Investigators, and staff from the Sponsor who have contact with subjects or Investigators or those who are involved in the direct conduct of the study until all planned randomized subjects complete the study and the final database lock has occurred.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 should be excluded from PP analysis set. Any randomized subjects who are discontinued from the study for any reason and have at least a post-baseline efficacy data should be included in the MITT analysis set using Last observation carried forward (LOCF) method. LOCF method will be used as an imputation method for the efficacy variables for MITT analysis.

8.4 RANDOMIZATION

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

8.5 DETERMINATION OF SAMPLE SIZE

This proof of concept study will include a total 36 subjects. Subject will be enrolled in 1:1:1 ratio to have 12 subjects in each arm i.e., Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg and placebo. Six patients in each group are planned for pharmacokinetic assessment therefore a total of 18 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. Additional patients will be enrolled if the dropout rate is more than 20%.

9 ADMINISTRATIVE MATTERS

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

9.1 ETHICS

9.1.1 Institutional Committee Review and Communications

The 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 USFDA-registered IEC/IRB. Should a protocol amendment be written 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 providing 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 accepted 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 his / her medical records may be examined by authorised monitors or Clinical Quality Assurance auditors appointed by the Sponsor, by appropriate IEC / IRB members and by inspectors from regulatory authorities.

Should a protocol amendment be made, the 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 DATA MANAGEMENT AND RECORDKEEPING

9.2.1 Drug Accountability

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

The Investigator and/or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the Sponsor or alternative disposition of unused product(s). These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the IP(s) and trial subjects. Investigators will maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all IP(s) received from the Sponsor.

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). Unused drug supplies will be destroyed at the site

after approval for the same by the Sponsor. No study drug will be destroyed or returned until drug accountability has been performed by the study monitor.

9.2.2 Patient Card

Upon enrolment in the study, patients will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

9.2.3 Data Management

9.2.3.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs 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.

9.2.3.2 Computer Systems

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

9.2.3.3 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.

9.2.3.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for adverse events and medical history, and

- WHO Drug Dictionary for prior and concomitant medications.

9.2.3.5 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.

9.2.4 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Data reported on the eCRFs that are derived from source documents (SDs) must be consistent with the SDs 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:

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

- Conclusion of subject'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 SDs, 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 enrolment of any patient in this study, the Sponsor or their designee 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 designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA 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.

9.3 QUALITY ASSURANCE AUDIT

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

9.4 PROCEDURES

9.4.1 Adverse Events

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

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

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

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

9.4.2 Serious Adverse Event

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

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

Serious Adverse Event Reporting-Procedures for Investigators:

Initial Reports:

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

Additionally, any serious adverse event, considered by an Investigator who is a qualified physician to be related to the Sponsor’s product that is brought to the attention of the Investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, CRO/Sponsor Safety personnel

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

Safety Contact Information:

Dr. Deven V Parmar, MD

[redacted]

Follow-Up Reports

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

9.4.3 Evaluating Adverse Events

An Investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 4. The Investigator's assessment of causality is required for each adverse event. Refer to Table 4 for instructions in evaluating adverse events.

Table 4. Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the Investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a pre-existing condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an Investigator who is a qualified physician. The Investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the Investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another aetiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent

		disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an Investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

All AEs, serious and non-serious, will be fully documented on the appropriate eCRF(s). For each AE, the Investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the IP. The Investigator will determine the relationship of the IP to all AEs.

Fatal or life-threatening, unexpected adverse drug reactions (ADRs) occurring in *clinical investigations* qualify for expedited reporting. Regulatory agencies shall be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days.

Serious, unexpected ADRs that are not fatal or life-threatening must be filed with the regulatory agency as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

9.4.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hrs to CRO/Sponsor Clinical Safety following the same procedures as outlined in Section 9.4.2. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

9.4.5 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 IB.

9.4.6 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.

Although pregnancy and lactation are not considered adverse events, 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. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

The investigator should report the pregnancy to CRO/Sponsor Clinical Safety within 24 hours of being notified. CRO/Sponsor Clinical Safety will then forward the Exposure In Utero form to the investigator for completion.

9.5 RULES FOR AMENDING PROTOCOL

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

9.6 FINANCIAL DISCLOSURE

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfil its obligations under 21 CFR §54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study. Details of insurance coverage will be covered in separate document/CTA/agreement.

9.7 DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment 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.

9.8 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions of participating physicians, 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.

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

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

9.9 FINAL REPORT AND PUBLICATION POLICY

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

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

9.10 ARCHIVING

Subject's files, identification codes and other source data (including original reports of test results, dispensing logs, records of informed consent), IEC/IRB approval letter, correspondence and other documents pertaining to the conduct of the 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.

10 REFERENCES

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11 APPENDICES

1. PBC-40 Questionnaire

Jacoby A, Rannard A, Buck D, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut 2005;54:1622–1629.

2. Normal Reference Range of Laboratory Parameters

12 SIGNATURE PAGE(S)

Protocol Title: A Phase 2, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability and Efficacy of Saroglitazar Magnesium in Patients with Primary Biliary Cholangitis (**EPICS**)

RESPONSIBILITY	NAME AND DESIGNATION	DATE AND SIGNATURE
SPONSOR'S MEDICAL EXPERT AND MONITOR, STUDY DIRECTOR (SPONSOR'S REPRESENTATIVE) AND MANAGEMENT APPROVAL	Dr. Deven V Parmar, MD [redacted]	[redacted] 21 Aug 2019

SPONSOR APPROVAL

STUDY TITLE: A Phase 2, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability and Efficacy of Saroglitazar Magnesium in Patients with Primary Biliary Cholangitis **(EPICS).**

I have read, understood and approve this protocol.

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

Date: 21 Aug 2019

AUTHORIZED SIGNATORY

Dr. Deven Parmar

DECLARATION OF PRINCIPAL INVESTIGATOR

STUDY TITLE: A Phase 2, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety, Tolerability and Efficacy of Saroglitazar Magnesium in Patients with Primary Biliary Cholangitis **(EPICS).**

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

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

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

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

Name of the Principal Investigator:

Name and Address of the site:

Contact Details:

_____ _____/_____/_____
Signature **Date**

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