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STATISTICAL ANALYSIS PLAN

NCT03061721

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

Version: Final 1.0

Date: 19/Oct/2018

[redacted]

Statistical Analysis Plan

[redacted]

SIGNATURE PAGE – ZYDUS DISCOVERY DMCC

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

[redacted]

26/10/18

Dr. Deven Parmar MD **Date (DD/MM/YY)**

Head - Clinical R & D

[redacted]

Statistical Analysis Plan

[redacted]

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

[redacted]

29 Oct 2018

Senior Biostatistician **Date (DD Mmm YY)**

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ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ATC	Anatomical therapeutic chemical
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
Bpm	Beats per minute
CI	Confidence interval
CSP	Clinical Study Protocol
CS	Clinically significant
CV	Coefficient of variation
DBP	Diastolic blood pressure
ECG	Electrocardiogram
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NK	Not known
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation or single dose
SE	Standard error of the mean
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

Abbreviation / Acronym	Definition / Expansion
WHO-DD	World Health Organisation - Drug Dictionary

STATISTICAL ANALYSIS PLAN

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables, populations, anticipated data transformations and other details of the analyses not provided in the Clinical Study Protocol (CSP).

The analyses described are based on the final 3.0 CSP, dated, 26/Mar/2018.The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in a SAP Addendum.

1. STUDY OBJECTIVES

1.1 Primary Objective

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

1.2 Secondary Objective

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

- Pharmacokinetics of Saroglitazar Magnesium following first dose and last dose.
- Quality of life (QoL)
- Safety and tolerability of repeat dosing of 1 mg, 2 mg or 4 mg Saroglitazar Magnesium.

1.3 Exploratory Objective

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

2. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study in up to 104 patients with a diagnosis of NAFLD and/or NASH. The study will be conducted over a period of up to 22 weeks and will include an optional Pre-screening, a Screening Phase (Days -35 to -7), a 16-week Treatment Phase following randomization on Day 1 to either Saroglitazar Magnesium (1 mg, 2 mg or 4 mg) or placebo orally once daily in the morning before breakfast.

Pre-screening

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

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

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

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

Screening Phase:

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

Visit 2 (Day -14 to -7): Liver enzymes (AST, ALT, ALP and total bilirubin (TB) will be re-measured approximately 3 weeks from Day -35 to determine eligibility. Elevated ALT ≥50 U/L on 2 occasions in the Screening is necessary for study entry. The variance in the levels of the repeat measures of serum ALT and total bilirubin (TB) at Day -14 (Visit 2) must be ≤30%, compared to the Day -35 (Visit 1) levels to be eligible for study entry.

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

Treatments:

- Treatment A= Saroglitazar Magnesium 1 mg
- Treatment B = Saroglitazar Magnesium 2 mg
- Treatment C = Saroglitazar Magnesium 4 mg
- Placebo = Placebo

Randomization & Treatment Phase:

The Randomization & Treatment Phase will include 5 additional outpatient visits over a period of 16 weeks including the randomization visit. Efficacy assessments will be conducted on these 5 visits by measuring liver enzymes (AST, ALT, ALP and TB), CK-18 fragments, ELF, fasting glucose, serum insulin levels, lipoprofile, homeostasis model assessment (insulin resistance

[HOMA-IR]) and homeostasis model assessment (β cell function [HOMA-β], liver stiffness and CAP by transient elastography/FibroScan, liver fat content with MRI-PDFF and QoL. In addition, safety assessments will be conducted and there will be no clinically significant changes in dietary, physical activity or alcohol consumption.

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

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

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

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

Table 1 Schedule of Assessments

[redacted]

[redacted]

[redacted]

3. STUDY POPULATION

The study population will consist of 104 patients (with NAFLD and/or NASH who have elevated ALT (defined as ≥50 U/L at the Screening Visits)). Patients will be eligible for the study if they meet all of the inclusion criteria and none of the exclusion criteria. Detailed lists of inclusion and exclusion criteria are shown in Sections 4.2 and 4.3 of the CSP.

4. STATISTICAL BASIS FOR SAMPLE SIZE

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

Descriptive statistics was calculated for the percentage change from baseline to Week 12 in serum ALT levels from a clinical study on Saroglitazar Magnesium in NASH patients [redacted]

Sample size is based on a 1-sided t-test (2 independent samples) at the 5% significance level for the percentage change from baseline between Saroglitazar Magnesium (1 mg, 2 mg and 4 mg) and placebo at Week 12 (a 1 sided test ignores the small probability of a significant result in the "wrong" direction [i.e., superiority of placebo over Saroglitazar Magnesium]. Because this is a proof-of-concept (PoC) study, this approach is acceptable).

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

5. RANDOMIZATION

5.1 Screening Numbers

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

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

Block randomization of patients to treatment (Placebo, Saroglitazar Magnesium 1 mg, 2 mg or 4 mg) will occur in 1:1:1:1 ratio. The block randomization was generated following biostatistics procedure for generation of randomization lists. Each block contained investigational medicinal products; Saroglitazar Magnesium 1 mg, 2 mg, 4 mg and placebo. Each block (outer carton) contain 4 boxes (inner cartons) of study drug (enough for 4 patients).

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

5.3 Patient Replacements

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

6. STATISTICAL ANALYSIS CONVENTIONS

6.1 Analysis Variables

6.1.1 Medial History, Demographic and other Baseline Variables

The medical history comprises:

Medical history (including start and stop date or whether the condition is ongoing)

- Medical history
- Medication history

- Reproductive history

The following demographic and baseline information will be recorded:

- Date of informed consent
- Age (yrs)
- Gender
- Ethnic origin (Hispanic/Latino, Not Hispanic/not Latino, Not Reported, Unknown).
- Race (White, American Indian/Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Black/African American, Other)
- Height (cm) (without shoes)
- Weight (kg) (without shoes)
- BMI

Other baseline characteristics will be recorded as follows:

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

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version **19.1** or later.

6.1.2 Safety Variables

6.1.2.1 Adverse Events

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

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

Treatment Emergent Adverse Event

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

Severity and Relationship to Study Medication

All AEs must be recorded on the appropriate AE CRF for the patient. All AEs must be reported whether or not considered causally related to study drug. For every AE, the PI will provide an assessment of the severity and causal relationship to study drug, will document all actions taken with regard to study drug, and will document any other treatment measures for the AE.

Serious adverse events (SAEs)

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

TEAE leading to discontinuation

If the patient discontinued due to an AE, as indicated by the investigator from the Study Conclusion page of the eCRF where primary reason for withdrawal is “Adverse Event” then the TEAE is considered as TEAE led to discontinuation of study. All adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, last version available before database lock).

If the relationship is unknown the relationship will be imputed with “Related”. Any AE recorded with an unknown seriousness will be regarded as a SAE for the tabulations.

There will be no imputation of missing or partial AE date and it will be shown as NK for the listings.

AEs with missing start dates/times will be handled as follows for the treatment-emergent based tabulations:

- Missing start date:
  - If the start date is completely missing but the end date is known and shows that the AE ended on or after the dosing date in a specific treatment group, then the start date will be imputed as the day of dosing in that treatment group
  - If the end date is known and shows that the AE ended before the first dosing date then the screening date will be used for the start date
- Missing start day:
  - If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before a dose was given in that month; in which case the date will be imputed as 01
  - If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01
- Missing start day and month:
  - If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later
- Missing times
  - Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

Adverse events with completely unknown start dates will be considered as treatment-emergent for the tabulations. Adverse events with missing start/ stop date will be considered as treatment-

emergent unless the partial date excludes that possibility, e.g. the AE month is prior to the month in which treatment started. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months.

Start and stop dates for prior/ concomitant medication will also be treated similarly for tabulations as mentioned above for treatment-emergent AEs.

6.1.2.2 Clinical Laboratory Tests

Laboratory tests will be performed at the following time points (unless otherwise stated below):

- Pre-screening
- Screening (Visit 1 and Visit 2)
- Week 0 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6)
- End of Treatment (Week 16/Visit 7)

The following safety laboratory parameters will be measured:

Hematology:	Erythrocytes, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, Platelets, Leukocytes, Hemoglobin, Hematocrit, Prothrombin Time (PT), International Normalized Ratio (INR).
Clinical chemistry:	Albumin, Blood Urea Nitrogen (BUN), Creatinine, Creatinine Phosphokinase (CPK), high-sensitive C-Reactive Protein (hs-CRP), Triglycerides, Urea, Uric Acid, Cholesterol **Electrolytes:** Sodium, Potassium **Liver Enzymes:** Alanine Aminotransferase (ALT), Aminotransferase (AST), Alkaline Phosphatase (ALP), Bilirubin, γ-Glutamyl Transferase (GGT), Serum proteins
Urinalysis:	Appearance, color, Bilirubin, pH, Protein, Glucose, Ketones, leukocytes, Blood, Nitrite, Specific Gravity, Urobilinogen
Serology:	Human Immunodeficiency Virus (HIV) type 1 and type 2, Anti-Hepatitis A virus (HAV IgM), Hepatitis B Virus Surface Antigen (HBsAg), Hepatitis C Virus Antibody (HCV)
Pregnancy test:	For women of childbearing potential only at the first Screening Visit: Serum Pregnancy test at screening (Visit 1/Day -35) and urine Pregnancy test at week 0 (Visit 3), week 4 (Visit 4), week 8 (Visit 5), week 12 (Visit 6) and week 16 (Visit 7) (end of treatment).

Drugs-of-abuse Screening (Urine)	**Screening Phase [Day -35]:** Amphetamines, Benzodiazepines, Marijuana, Cocaine, Opioids

6.1.2.3 Vital Signs

Measurement of vital signs will be performed at the following time points (unless otherwise stated below):

- Screening (Visit 1/Day -35)
- Week 0 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6)
- End of Treatment (Week 16/Visit 7)

The following vital signs measurements will be obtained:

- Sitting blood pressure (Systolic (SBP) and diastolic (DBP); mmHg) (measured in triplicate, approximately 2 minutes apart at the Screening Visit and a single measurement at all other visits)
- Pulse (beats per minute) (measured in triplicate, approximately 2 minutes apart at the Screening Visit and a single measurement at all other visits)
- Oral body temperature [°F or °C] (single measurement at all visits)
- Respiratory rate (breaths per minute) (single measurement at all visits)

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

6.1.2.4 Electrocardiograms

Measurement of 12-lead ECGs will be performed at the following time points:

- Screening (Visit 1/Day -35)
- Week 0 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6)
- End of Treatment (Week 16/Visit 7)

The following ECG parameters will be recorded:

- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- corrected QT interval (QTc)
- Heart rate (bpm)

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

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'.

6.1.2.5 Physical Examination

Physical examination will be performed at the following time points:

- Screening (Visit 1/Day -35)
- Week 0 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 5), Week 12 (Visit 6)
- End of Treatment (Week 16/Visit 7)

The physical examination will include the following: General appearance, Eyes, Ears/Nose/Throat, cardiovascular, respiratory, abdominal, genitourinary, skin/mucosa, musculoskeletal, neurological, and lymphatic system.

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

The Investigator will mark the physical findings as normal, abnormal or not done and the Investigator will assess abnormal results as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS' in the CRF, including details of any abnormality.

6.1.2.6 Prior and Concomitant Medication

Prior medications and concomitant treatments (if any) will be coded according to the World Health Organization Drug Dictionary (WHO Drug Dictionary, latest version before database lock). These

will be classified by Anatomical Therapeutic Chemical (ATC) categories and listed separately for each patient.

6.1.3 Pharmacokinetic Variables

Not applicable in this plan.

6.1.4 Pharmacodynamic Variables

Not applicable.

6.1.5 Efficacy Variables

6.1.5.1 Blood Samples

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

Serum alanine aminotransferase (ALT) levels.

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

Lipoprofile: includes fasting (at least 8 hours) LDL, VLDL, HDL, total cholesterol, non-HDL cholesterol, apo A1 and apo B. The results of the lipoprofile (except total cholesterol) will be blinded to site. Serum triglyceride results will not be blinded.

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

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

6.1.5.2 Quality of Life

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

role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health.

The two component scores will include:

Physical Component Summary: Summarizes the physical components of the SF-36V2: Physical Functioning, Role-Physical, Bodily Pain and General Health.

Mental Component Summary: Summarizes the mental component of the SF-36V2: Vitality, Social Functioning, Role Emotional and Mental Health.

6.1.5.3 Transient Elastography/FibroScan

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

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

The magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) is a novel imaging-based biomarker that allows fat mapping of the entire liver. Liver fat content will be measured using MRI-PDFF. PDFF technique is an MRI protocol that improves on the conventional Dixon in- and out-of-phase method.

6.2 Analysis Populations

6.2.1 Randomized Set

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

6.2.2 Safety Analysis Set

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

6.2.3 Full Analysis Set (FAS)

The FAS will consist of all patients who have been randomized, taken at least 1 dose of the study treatment and have provided efficacy data for at least 1 endpoint. Patients who receive study drug

different from that to which they are randomized will be included in the group to which they are randomized.

The primary analysis population for this study is defined by the full analysis set of patients.

6.2.4 Per Protocol (PP) Analysis Set

The PP Analysis Set will consist of all patients in the FAS who have additionally completed the double-blind treatment phase and have not deviated from or violated the protocol in such a way that could affect efficacy outcome. Patients will be grouped according to the actual treatment received. The PP Analysis Set will be defined before un-blinding the study.

6.2.5 Enrolled Set

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

6.2.6 Pharmacokinetic Population

Pharmacokinetic population will include randomized patients with evaluable concentration profiles and do not have any major protocol deviations that could affect the PK profile of the treatment.

6.2.7 Treatment misallocations

If a patient was,

- Randomized but not treated: patient will appear on the patient evaluation table as randomized but not treated; this is the extent of how much the patient will be reported.
- randomized but took at least one dose of incorrect treatment, then the patient will be reported under the randomized treatment group for all efficacy and safety analyses as part of the FAS and Safety analyses, but omitted from PP analyses.

6.3 Statistical Analysis Methods

6.3.1 Listings and Descriptive Statistics

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics, unless stated otherwise.

Frequency counts (number of subjects [n] and percentages) will be presented for each qualitative variable. Descriptive statistics (n, mean, SD, median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if n ≥3.

The following rules will apply to any repeated safety measurements:

- If the repeated measurement occurs prior to IMP administration in each treatment group, then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement occurs after IMP administration in each treatment group, then the first (non-missing) value of any repeated measurements will be used in descriptive statistics and in the calculation of changes from baseline.

All descriptive statistics will be presented by treatment for measurements obtained during each treatment group. The baseline for all measurements (where applicable) will be the last pre-dose measurement within each treatment group while values at Day -14 to -7 (Visit 2) will be considered as baseline for the efficacy assessment of liver function tests. Descriptive statistics for all data obtained at Screening and follow-up will be presented separately.

6.3.2 Statistical Significance Level

All statistical tests will be one-sided and will be performed at the 5% level of significance, unless otherwise stated.

6.3.3 Software

All statistical analyses will be performed using Statistical Analysis Software (SAS®) Version 9.2 or later. The PK analysis will be performed using Phoenix® WinNonlin® professional software (Version 6.4 or higher).

6.3.4 Missing Data

Last observation carried forward (LOCF) method will be used to impute missing values for the efficacy variables for the FAS population. Only post-baseline values will be carried forward. If no post-baseline value is present then no imputation will be done and baseline value will not be carried forward.

No imputation method will be employed for drug concentration or PK parameters. Data from any subject with missing concentration values (missed blood samples, lost samples, samples unable to be quantitated) may be used if pharmacokinetic parameters can be adequately estimated using the remaining data points, otherwise that subject will be excluded from specific pharmacokinetic parameter that cannot be estimated.

6.3.5 Interim Analysis

Not applicable

6.3.6 Patient Disposition

The number of patients who will be enrolled into the study, patients included in each analysis set, and subjects who completed/prematurely discontinued the study, as well as the reason for discontinuation, will be presented by treatment and overall using counts and percentages [Table 14.1.1, Table 14.1.2].

Patient disposition will be listed by treatment group and patient number. It will include whether study was completed as per protocol, date of discontinuation, reason for discontinuation and comment on discontinuation [Listing 16.2.1.1].

Patient assignment to analysis populations will be listed by patient number [Listing 16.2.3.1].

6.3.7 Protocol Deviations

All protocol deviations as recorded in the protocol deviations log will be listed by patient number and will include a category of deviation, description of the deviation, the date/time of the deviation, study day of the deviation, time point, classification (Major/Minor) and led to exclusion of population if any [Listing 16.2.2.1] and will be summarized by treatment group [Table 14.2.2].

6.3.8 Demographic Data and other baseline characteristics

Demographic variables (gender, race, ethnicity, age, height, weight, BMI) will be listed by treatment group and patient number [Listing 16.2.4.1]. Demographic variables will be summarized by treatment group for each for Safety, FAS, PP and PK [Table 14.1.2.1 (Safety), Table 14.1.2.2 (FAS), Table 14.1.2.3 (PP), Table 14.1.2.4 (PK)].

Medical history will be listed by patient number and medical history term. It will include the following: condition/disease, start date and stop date (or ongoing if applicable) [Listing 16.2.4.2].

Reproductive history will be listed by patient number [Listing 16.2.4.4].

Informed consent history will be listed by patient number and will include the date of consent and whether consent was obtained [Listing 16.2.1.2].

Study visits will be listed by treatment and patient number [Listing 16.2.1.3].

Failed Inclusion and exclusion criteria will be listed by patient number which will include screen failures as well [Listing 16.2.1.4].

Randomization of patients will be listed by patient number and will include randomization number, planned treatment, actual treatment received and replacement patient number if any [Listing 16.2.1.5].

Other baseline characteristics data will be listed by treatment group and patient number as follows:

- Alcohol, tobacco history and caffeine usage history [Listing 16.2.4.3]
- Diet, Physical activity and alcohol [Listing 16.2.4.4]

6.3.9 Prior and Concomitant Medication

Prior and concomitant medication will be listed by treatment group, patient number and will include the following information: medication name, start date/time of medication, stop date/time of medication, whether the medication is ongoing, dose per intake, unit, route, frequency, indication. If the date/time cannot be used to determine whether the medication is prior or concomitant, then the information would be missing for category of medication (Prior/Concomitant) in the concomitant medication listing [Listing 16.2.4.5] and will be summarized by treatment group [Table 14.3.4.1].

6.3.10 Exposure to the study drug and compliance

Exposure to study drug and compliance information will be recorded and will be listed by treatment group and patient number [Listing 16.2.5.1 and Listing 16.2.5.2] and will be summarized by treatment group [Table 14.3.4.2 and Table 14.3.4.3].

6.3.11 Pharmacokinetic Concentrations and Variables

Not applicable in this plan.

6.3.12 Safety Analysis

The analysis of the safety variables will be based on the safety population. All safety parameters will be listed by treatment group and patient number.

6.3.12.1 Adverse Events

Adverse events will be listed by patient number [Listing 16.2.7.1]. The number and percent of patients experiencing an event will be tabulated for each system-organ class, preferred term by treatment group [Table 14.3.1.1].

Adverse events will also be tabulated according to causality [Table 14.3.1.2] and severity by treatment group [Table 14.3.1.3].

The Adverse Events leading to discontinuation and SAEs will also be summarized by treatment group [Table 14.3.1.4].

Adverse Events leading to discontinuation [Listing 14.3.2.1] and SAEs will be listed [Listing 14.3.2.2] by patient number.

6.3.12.2 Clinical Safety Laboratory Tests (hematology, biochemistry and urinalysis)

Individual data listings of laboratory results for observed and change from baseline (biochemistry [Listing 16.2.8.1], hematology [Listing 16.2.8.2] and urinalysis [Listing 16.2.8.3]) will be listed by treatment group, patient number, laboratory parameter and study visit/time point.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. The All the laboratory abnormal results will be assessed by the Investigator and will be reported as abnormal not clinically significant (NCS) or abnormal clinically significant (CS) by the Investigator. Clinically significant laboratory values will be recorded by the Investigator as AEs.

Descriptive statistics (biochemistry [Table 14.3.5.1] and hematology [Table 14.3.5.2]) will be presented for observed results and change from baseline by treatment group (n, mean, SD, median, minimum, maximum).

Each post-treatment assessment will be presented in shift tables (biochemistry [Table 14.3.5.3] and hematology [Table 14.3.5.4]) for categorized laboratory results (normal, low and high). Shift table for qualitative variables (Urinalysis) will be presented in Table 14.3.5.5 for laboratory results (abnormal and normal).

Additional individual data listings will be presented by patient number as following:

- Childbearing potential and Pregnancy [Listing 16.2.8.4].
- Serology [Listing 16.2.8.5]

6.3.12.3 Vital Signs

Individual data listings of vital signs (observed and change from baseline) will be presented by treatment group, parameter and patient number [Listing 16.2.9.1]. Individual clinically significant vital sign findings that were considered AEs by the Investigator will be presented in the AE listings.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for observed values as well as change from baseline data values will be presented by treatment group and parameter [Table 14.3.6.1].

6.3.12.4 Twelve-Lead Electrocardiogram

Twelve-lead ECG data (observed and change from baseline) will be listed [Listing 16.2.9.2] by treatment group, parameter, patient number and visit/time point.

Descriptive statistics (n, mean, SD, median, minimum, maximum) for observed values will be presented by treatment group and parameter [Table 14.3.6.2].

6.3.12.5 Physical Examination

The abnormal physical exam findings will be listed by treatment group, parameter, patient number and visit/time-point [Listing 16.2.9.3].

6.3.13 Efficacy Analysis

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

Individual data listings of efficacy variables (observed, absolute change from baseline, percentage change from baseline) will be presented by treatment group, efficacy parameter, patient number and visit/time point. Observed, absolute change, percentage change from baseline values will be summarized (n, mean, standard deviation, median, minimum and maximum) for each efficacy parameter by treatment group and at each visit/time point without covariate adjustment.

Primary Efficacy Variable: serum ALT levels [Listing 16.2.6.1 and Table 14.2.1.1, Table 14.2.1.2]

Secondary and exploratory efficacy variables:

- **Insulin resistance and glycemic control:** includes fasting (at least 8 hours) insulin, fasting plasma glucose, HbA1c, C-peptide, HOMA-IR and HOMA-ß [Listing 16.2.6.9 and Table 14.2.4.7, Table 14.2.4.8]. Graphical representation of mean absolute, mean change and mean percent change from baseline of insulin resistance (IR) by treatment will be presented [Figure 14.2.1.10, Figure 14.2.1.11, Figure 14.2.1.12]. Graphical representation of mean absolute, mean change and mean percent change from baseline of glycemic control by treatment will be presented [Figure 14.2.1.13, Figure 14.2.1.14, Figure 14.2.1.15].

- **Lipoprofile:** includes fasting (at least 8 hours) LDL, VLDL, HDL, total cholesterol, non-HDL cholesterol, apo A and apo B [Listing 16.2.6.8 and Table 14.2.4.5, Table 14.2.4.6]. Graphical representation of mean absolute, mean change and mean percent change from baseline lipids and lipoprofiles by treatment will be presented [Figure 14.2.1.7, Figure 14.2.1.8, Figure 14.2.1.9].

- **CK-18 and APRI:** includes CK-18, AST and platelet count [Listing 16.2.6.3, Listing 16.2.6.5 and Table 14.2.3.3, Table 14.2.3.4, Table 14.2.3.7, Table 14.2.3.8].

- **ELF score:** serum samples. Enhanced liver fibroses score is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease [Listing 16.2.6.4 and Table 14.2.3.5, Table 14.2.3.6].

Quality of life:

Subjective QoL assessments will be measured using the SF-36 version 2.0, which is a 36-item patient response questionnaire that measures QoL across 8 domains, both physically and emotionally based. The 8 domains are physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health [Listing 16.2.6.10, Listing 16.2.6.11 and Table 14.2.5.1, Table 14.2.5.2].

Transient Elastography/FibroScan

Liver stiffness measurements will be performed by transient elastography using the FibroScan (Echosens, Paris, France). The appropriate FibroScan measurement probe should be used (i.e., M or XL) based on the manufacturer's recommendation for probe choice according to chest circumference and age. FibroScan is optional and performed only sites with machines available at sites [Listing 16.2.6.7 and Table 14.2.4.3, Table 14.2.4.4].

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

The magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) is a novel imaging-based biomarker that allows fat mapping of the entire liver. Liver fat content will be measured using MRI-PDFF. Proton-density-fat-fraction technique is an MRI protocol that improves on the conventional Dixon in- and out-of-phase method. Graphical representation of mean absolute, mean change and mean percent change from baseline of liver fat content by treatment will be presented [Listing 16.2.6.2 and Table 14.2.1.3, Table 14.2.1.4 and Figure 14.2.1.4, Figure 14.2.1.5, Figure 14.2.1.6].

6.3.13.1 Primary Efficacy Analyses

The primary analysis for the primary efficacy endpoint will be based on the FAS.

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

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

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

and

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

where $\mu_{\text{treatment group}}$ is the mean percent change from baseline to Week 16 in serum ALT levels with Saroglitazar Magnesium (1 mg, 2 mg and 4 mg) or placebo.

Note: Improvement in percent change from baseline to Week 16 in ALT levels is indicated by $\mu_{\text{treatment group}} < 0$.

Hypotheses will be tested at a 1-sided nominal significance level-alpha of 0.05.

Least squares (LS) means for each treatment group and associated standard errors will be derived. Differences in LS means and associated 2-sided 90% confidence intervals will be obtained using ANCOVA and tabulated [Table 14.2.1.1]. One-tailed p-value will be presented to test the alternative hypothesis that Saroglitazar Magnesium is superior to placebo.

Graphical representation of mean absolute, mean change and mean percent change from baseline at Week 16 in for liver enzymes levels for different treatment groups will be presented [Figure 14.2.1.1, Figure 14.2.1.2 and Figure 14.2.1.3]

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

Due to this being a proof-of-concept (PoC) study, no adjustment of any p-values will be presented to account for inflation of the Type 1 error rate.

Secondary analyses (of the primary endpoint) will be analyzed using a similar analysis in the PP Analysis Set [Table 14.2.1.2].

The following SAS code will be used for analyses of primary endpoint:

```
Proc Mixed data= eff (where= (visit='Week 16'));
  Class treatment subject;
  model Percent =treatment baseline;
  Lsmeans treatment / alpha=0.10 cl pdiff;
  Estimate "Treatment A – Placebo" treatment 1 0 0 -1/ cl alpha=0.10;
  Estimate "Treatment B – Placebo" treatment 0 1 0 -1/ cl alpha=0.10;
  Estimate "Treatment C – Placebo" treatment 0 0 1 -1/ cl alpha=0.10;
  ods output estimates=estim lsmeans=ls_means;
run;
```

Similar set of SAS statements will be used for estimating significance of change from baseline between the treatment arms.

Residual analysis will be used to check assumptions for the ANCOVA model. Normality of residuals will be performed by using Shapiro-Wilk test. Should any of the assumptions of the analysis method not be adequately met, an alternative procedure will be used and fully documented.

6.3.13.2 Secondary Efficacy Analyses

For each endpoint, the comparison will be conducted using a significance level (alpha) set at 0.10 (2-sided) or equivalently 0.05 (1-sided).

- Change in liver fat at Week 16 as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF)
- Percentage change from baseline and absolute change from baseline in serum ALT levels at Week 4, week 8 and Week 12 of treatment
- Percentage change from baseline and absolute change from baseline in CK-18 fragment, ELF score and APRI at Week 8, and Week 16 after treatment
- Absolute change from baseline in AST/ALT ratio at Week 4, Week 8, Week 12 and Week 16 after treatment
- Pharmacokinetics of Saroglitazar following first dose and last dose in approximately 32 patients (approximately 8 from each dose arm) with NAFLD/NASH
- Absolute Change from baseline in the SF-36 8 domain scores and 2 component scores (separate analyses) at Week 16 after treatment.
- Proportions of patients with percentage reductions of ≥ 25% and ≥ 50% from baseline in ALT levels at Week 4, Week 8, Week 12 and Week 16 will be analyzed using Chi-square test/ Fisher exact test by comparing treatment group to placebo group. The results will be tabulated with Chi-square coefficient, p-value and 90% confidence interval.

The following SAS code will be used for secondary analyses except for proportions:

```
Proc Mixed data= eff;
   by visit;
   Class treatment subject;
   model Percent =treatment baseline;
   Lsmeans treatment / alpha=0.10 cl pdiff;
   Estimate "Treatment A – Placebo" treatment 1 0 0 -1/ cl alpha=0.10;
   Estimate "Treatment B – Placebo" treatment 0 1 0 -1/ cl alpha=0.10;
   Estimate "Treatment C – Placebo" treatment 0 0 1 -1/ cl alpha=0.10;
   ods output estimates=estim lsmeans=ls_means;
run;
```

Similar set of SAS statements will be used for estimating significance of change from baseline between the treatment arms.

The following SAS code will be used for secondary analyses for proportions:

```
Proc freq data=eff;
   by visit;
   Table param*trt/ nocum nopercent chisq;
   output out=ChiSqData n nmiss pchi;
run;
```

6.3.13.3 Exploratory Efficacy Analyses

The exploratory analyses will be done for the following end points using an analysis of covariance (ANCOVA) model with treatment as factor and baseline as covariate. The comparison of interest is Saroglitazar Magnesium 1 mg, 2 mg and 4 mg versus placebo.

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

The exploratory analyses will be based primarily on the FAS, and analyses based on the PP Analysis Set will be secondary to this. The same sas code as given in section 6.3.13.1 will be

considered for this exploratory analysis. The individual values of the exploratory endpoints will be listed by treatment group, patient number and summary statistics will be tabulated for each treatment group.

7. REFERENCES

1. SAS® Version 9.3 of the SAS System for Personal Computers. Copyright © 2002-2003. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.
2. WinNonlin Professional Software Version 6.3. https://www.certara.com/
3. Guidance for Industry. E9 Statistical Principles for Clinical Trials. CDER. September 1998

8. TABLES AND LISTINGS TO BE INCLUDED IN SECTION 14 OF THE CLINICAL STUDY REPORT

Baseline and Demographic Data

Table 14.1.1 Patient Disposition (Randomized set)

Table 14.1.2 Summary of screen failures (Enrolled set)

Table 14.1.2.1 Patient Demographics (Safety Population)

Table 14.1.2.2 Patient Demographics (FAS Population)

Table 14.1.2.3 Patient Demographics (PP Population)

Table 14.1.2.4 Patient Demographics (PK Population)

Pharmacokinetic Data

Not applicable in this analysis plan.

Efficacy Data

Table 14.2.1.1 Statistical Analysis of ALT percentage change from baseline to week 16 (FAS Population)

Table 14.2.1.2 Statistical Analysis of ALT percentage change from baseline to week 16 (PP Population)

Table 14.2.1.3 Statistical Analysis of change in liver fat from baseline to week 16 (FAS Population)

Table 14.2.1.4 Statistical Analysis of change in liver fat from baseline to week 16 (PP Population)

Table 14.2.1.5 Statistical Analysis of ALT change from baseline to week 4, Week 8, Week 12 & Week 16 (FAS Population)

Table 14.2.1.6 Statistical Analysis of ALT change from baseline to week 4, Week 8, Week 12 & Week 16 (PP Population)

Table 14.2.1.7 Statistical Analysis of proportion of patients who sustain a decrease in ALT from baseline to week 4, Week 8, Week 12 & Week 16 (FAS Population)

Table 14.2.1.8 Statistical Analysis of proportion of patients who sustain a decrease in ALT from baseline to week 4, Week 8, Week 12 & Week 16 (PP Population)

Table 14.2.1.9 Statistical Analysis of proportion of patients with ≥ 25% and ≥ 50% reduction in ALT from baseline to week 4, Week 8, Week 12 & Week 16 (FAS Population)

Table 14.2.1.10 Statistical Analysis of proportion of patients with ≥ 25% and ≥ 50% reduction in ALT from baseline to week 4, Week 8, Week 12 & Week 16 (PP Population)

Table 14.2.1.11 Statistical Analysis of change in CK-18 fragments from baseline to Week 8 and Week 16 (FAS Population)

Table 14.2.1.12 Statistical Analysis of change in CK-18 fragments from baseline to Week 8 and Week 16 (PP Population)

Table 14.2.1.13 Statistical Analysis of change in ELF score from baseline to Week 8 and Week 16 (FAS Population)

Table 14.2.1.14 Statistical Analysis of change in ELF score from baseline to Week 8 and Week 16 (PP Population)

Table 14.2.1.15 Statistical Analysis of change in APRI from baseline to Week 8 and Week 16 (FAS Population)

Table 14.2.1.16 Statistical Analysis of change in APRI from baseline to Week 8 and Week 16 (PP Population)

Table 14.2.1.17 Statistical Analysis of absolute change in AST/ALT ratio from baseline to week 4, Week 8, Week 12 & Week 16 (FAS Population)

Table 14.2.1.18 Statistical Analysis of absolute change in AST/ALT ratio from baseline to

week 4, Week 8, Week 12 & Week 16 (PP Population)

Table 14.2.1.19 Statistical Analysis of absolute change in QOL scores from baseline to Week 16 (FAS Population)

Table 14.2.1.20 Statistical Analysis of absolute change in QOL scores from baseline to Week 16 (PP Population)

Table 14.2.1.21 Statistical Analysis of change in liver stiffness/CAP from baseline to Week 16 (FAS Population)

Table 14.2.1.22 Statistical Analysis of change in liver stiffness/CAP from baseline to Week 16 (PP Population)

Table 14.2.1.23 Statistical Analysis of absolute change in fasting lipid and lipoprofiles from baseline to week 4, Week 8, Week 12 & Week 16 (FAS Population)

Table 14.2.1.24 Statistical Analysis of absolute change in fasting lipid and lipoprofiles from baseline to week 4, Week 8, Week 12 & Week 16 (PP Population)

Table 14.2.1.25 Statistical Analysis of absolute change in insulin resistance and glycemic control from baseline to Week 8 & Week 16 (FAS Population)

Table 14.2.1.26 Statistical Analysis of absolute change in insulin resistance and glycemic control from baseline to Week 8 & Week 16 (PP Population)

Table 14.2.2 Summary of Protocol deviation

Table 14.2.3.1 Summary of ALT levels (FAS Population)

Table 14.2.3.2 Summary of liver fat content measured by MRI-PDFF (FAS Population)

Table 14.2.3.3 Summary of CK-18 fragments (FAS Population)

Table 14.2.3.4 Summary of APRI (FAS Population)

Table 14.2.3.5 Summary of ELF Score (FAS Population)

Table 14.2.3.6 Summary of AST/ALT ratio (FAS Population)

Table 14.2.3.7 Summary of Insulin resistance and glycemic control (FAS Population)

Table 14.2.3.8 Summary of Lipids and Lipoprofile (FAS Population)

Table 14.2.3.9 Summary of Quality of Life - SF-36 domain and 2 components scores (FAS Population)

Safety Data

Table 14.3.1.1 Number and percent of patients with Adverse Events by System Organ Class, Preferred Term and Treatment (Safety Population)

Table 14.3.1.2 Number and percent of patients with Adverse Events by Treatment, System Organ Class, Preferred Term and Causality (Safety Population)

Table 14.3.1.3 Number and percent of patients with Adverse Events by Treatment, System Organ Class, Preferred Term and Severity (Safety Population)

Table 14.3.1.4 Summary of Adverse Events by Treatment (Safety Population)

Table 14.3.2.1 Adverse Events Leading to Discontinuation (Safety Population)

Table 14.3.2.2 Serious Adverse Events

Table 14.3.5.1 Summary of Biochemistry (Safety Population)

Table 14.3.5.2 Summary of Hematology (Safety Population)

Table 14.3.5.3 Summary of Biochemistry Shift Table (Safety Population)

Table 14.3.5.4 Summary of Hematology Shift Table (Safety Population)

Table 14.3.5.5 Summary of Qualitative parameters Shift Table (Safety Population)

Table 14.3.6.1 Summary of Vital Signs (Safety Population)

Table 14.3.6.2 Summary of Electrocardiogram (Safety Population)

Table 14.3.4.1 Summary of Concomitant Medication

Table 14.3.4.2 Summary of Exposure to study drug

Table 14.3.4.3 Summary of Compliance to study drug

9. FIGURES

10. LISTINGS TO BE INCLUDED IN SECTION 16 OF THE CLINICAL STUDY REPORT

Patient Disposition

Listing 16.2.1.1 Patient Disposition

Listing 16.2.1.2 Informed Consent

Listing 16.2.1.3 Study Visits

Listing 16.2.1.4 Failed Inclusion and Exclusion Criteria

Listing 16.2.1.5 Patient Randomization

Listing 16.2.2.1 Protocol Deviations

Listing 16.2.3.1 Assignment to Analysis Populations

Baseline and Demographic Data

Listing 16.2.4.1 Demographics

Listing 16.2.4.2 Medical History

Listing 16.2.4.3 Alcohol, smoking and caffeine usage history

Listing 16.2.4.4 Diet Physical Activity and Alcohol (DPA)

Concomitant Medication

Listing 16.2.4.5 Prior and Concomitant medication

Exposure

Listing 16.2.5.1 Exposure to study drug

Listing 16.2.5.2 Compliance

Pharmacokinetic Data

Not applicable in this analysis plan.

Pharmacodynamic Data

Not Applicable

Efficacy Data

Listing 16.2.6.1	Serum ALT levels
Listing 16.2.6.2	Liver Fat measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF)
Listing 16.2.6.3	Cytokeratin-18 [CK-18]
Listing 16.2.6.4	Enhanced liver fibrosis [ELF] score
Listing 16.2.6.5	Aspartate aminotransferase-to-platelet ratio index [APRI])
Listing 16.2.6.6	Serum AST/ALT ratio
Listing 16.2.6.7	Liver stiffness/CAP results measured by transient elastography/FibroScan®
Listing 16.2.6.8	Lipids and Lipoprofile parameters
Listing 16.2.6.9	Insulin resistance and glycemic control parameters
Listing 16.2.6.10	Individual Questions of QOL data
Listing 16.2.6.11	QOL data

Safety Variables

Listing 16.2.7.1	Adverse Events
Listing 14.3.2.1	Adverse Events leading to discontinuation
Listing 14.3.2.2	SAEs
Listing 16.2.8.1	Biochemistry
Listing 16.2.8.2	Hematology
Listing 16.2.8.3	Urinalysis

Listing 16.2.8.4 Pregnancy Test

Listing 16.2.8.5 Serology

Listing 16.2.9.1 Vital Signs

Listing 16.2.9.2 Electrocardiogram Parameters

Listing 16.2.9.3 Physical Examination

Listing 16.2.9.4 Electrocardiogram Parameters

11. DOCUMENTATION OF STATISTICAL METHODS

Appendix 16.1.9.1.1 Raw SAS output of: Table 14.2.1.1 Statistical Analysis of ALT percentage change from baseline to week 16 - (FAS Population)

Appendix 16.1.9.1.2 Raw SAS output of: Table 14.2.1.2 Statistical Analysis of ALT percentage change from baseline to week 16 - (PP Population)

Appendix 16.1.9.2.1 Raw SAS output of: Table 14.2.1.3 Statistical Analysis of change in liver fat from baseline to week 16 - (FAS Population)

Appendix 16.1.9.2.2 Raw SAS output of: Table 14.2.1.4 Statistical Analysis of change in liver fat from baseline to week 16 - (PP Population)

Appendix 16.1.9.3.1 Raw SAS output of: Table 14.2.1.5 Statistical Analysis of ALT change from baseline to week 4, Week 8, Week 12 & Week 16 - (FAS Population)

Appendix 16.1.9.3.2 Raw SAS output of: Table 14.2.1.6 Statistical Analysis of ALT change from baseline to week 4, Week 8, Week 12 & Week 16 - (PP Population)

Appendix 16.1.9.4.1 Raw SAS output of: Table 14.2.1.7 Statistical Analysis of proportion of patients who sustain a decrease in ALT from baseline to week 4, Week 8, Week 12 & Week 16 - (FAS Population)

Appendix 16.1.9.4.2 Raw SAS output of: Table 14.2.1.8 Statistical Analysis of proportion of patients who sustain a decrease in ALT from baseline to week 4, Week 8, Week 12 & Week 16 - (PP Population)

Appendix 16.1.9.5.1 Raw SAS output of: Table 14.2.3.1 Statistical Analysis of proportion of patients with ≥ 25% and ≥ 50% reduction in ALT from baseline to week 4, Week 8, Week 12 & Week 16 - (FAS Population)

Appendix 16.1.9.5.2 Raw SAS output of: Table 14.2.3.2 Statistical Analysis of proportion of patients with ≥ 25% and ≥ 50% reduction in ALT from baseline to week 4, Week 8, Week 12 & Week 16 - (PP

Population)

Appendix 16.1.9.6.1 Raw SAS output of: Table 14.2.3.3 Statistical Analysis of change in CK-18 fragments from baseline to Week 8 and Week 16 - (FAS Population)

Appendix 16.1.9.6.2 Raw SAS output of: Table 14.2.3.4 Statistical Analysis of change in CK-18 fragments from baseline to Week 8 and Week 16 - (PP Population)

Appendix 16.1.9.7.1 Raw SAS output of: Table 14.2.3.5 Statistical Analysis of change in ELF score from baseline to Week 8 and Week 16 - (FAS Population)

Appendix 16.1.9.7.2 Raw SAS output of: Table 14.2.3.6 Statistical Analysis of change in ELF score from baseline to Week 8 and Week 16 - (PP Population)

Appendix 16.1.9.8.1 Raw SAS output of: Table 14.2.3.7 Statistical Analysis of change in APRI from baseline to Week 8 and Week 16 - (FAS Population)

Appendix 16.1.9.8.2 Raw SAS output of: Table 14.2.3.8 Statistical Analysis of change in APRI from baseline to Week 8 and Week 16 - (PP Population)

Appendix 16.1.9.9.1 Raw SAS output of: Table 14.2.4.1 Statistical Analysis of absolute change in AST/ALT ratio from baseline to week 4, Week 8, Week 12 & Week 16 - (FAS Population)

Appendix 16.1.9.9.2 Raw SAS output of: Table 14.2.4.2 Statistical Analysis of absolute change in AST/ALT ratio from baseline to week 4, Week 8, Week 12 & Week 16 - (PP Population)

Appendix 16.1.9.10.1 Raw SAS output of: Table 14.2.4.3 Statistical Analysis of change in liver stiffness/CAP from baseline to Week 16 - (FAS Population)

Appendix 16.1.9.10.2 Raw SAS output of: Table 14.2.4.4 Statistical Analysis of change in liver stiffness/CAP from baseline to Week 16 - (PP Population)

Appendix 16.1.9.11.1 Raw SAS output of: Table 14.2.4.5 Statistical Analysis of absolute

change in fasting lipid and lipoprofiles from baseline to week 4, Week 8, Week 12 & Week 16 - (FAS Population)

Appendix 16.1.9.11.2 Raw SAS output of: Table 14.2.4.6 Statistical Analysis of absolute change in fasting lipid and lipoprofiles from baseline to week 4, Week 8, Week 12 & Week 16 - (PP Population)

Appendix 16.1.9.12.1 Raw SAS output of: Table 14.2.4.7 Statistical Analysis of absolute change in insulin resistance and glycemic control from baseline to Week 8 & Week 16 - (FAS Population)

Appendix 16.1.9.12.2 Raw SAS output of: Table 14.2.4.8 Statistical Analysis of absolute change in insulin resistance and glycemic control from baseline to Week 8 & Week 16 - (PP Population)