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Document Title:	Statistical Analysis Plan		
Version Number:	2.0	Date:	11 Nov 2019
Protocol Number:	SARO.16.004	Sponsor Name:	Zydus Discovery DMCC

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)

Statistical Analysis Plan

(SARO.16.004)

Version 2.0

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Reviewer [redacted] Nov 11, 2019

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0. REVISION HISTORY

This is the first revision (Version 2.0) to the Statistical Analysis Plan dated April 03, 2018. This revision was conducted to include an interim analysis that will be conducted when approximately 24th active randomized subject completes the study as per the protocol amendment version 6.0, dated August 21, 2019.

1. INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from SARO.16.004 study. This document is based on protocol version 6.0. The statistical planning and conduct of analysis of the data from this study will follow the principles defined in relevant International Conference of Harmonization (ICH)-E9 guidelines. If more appropriate analytic procedures become available during the study, the statistical analysis plan (SAP) may be revised. Any revisions to the SAP (both alternative and additional methods) will be made prior to database lock and reasons for such revisions will be described in the final Clinical Study Report.

2. STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

Primary Objective

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 (PBC).

Secondary Objectives

- To compare the effect of Saroglitazar magnesium (2 mg and 4 mg) and placebo on below mentioned parameters following a 16-week treatment in patients diagnosed with PBC:
  - Alkaline Phosphatase
  - Lipids profile: TG, TC, HDL, LDL, and VLDL
  - Liver biochemistries: GGT, ALT, AST, bilirubin and albumin.
  - Serum total bile acids
  - 7α-hydroxy-4-cholesten-3-one (C4)
  - Fibroblast growth factor 19 (FGF19)

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

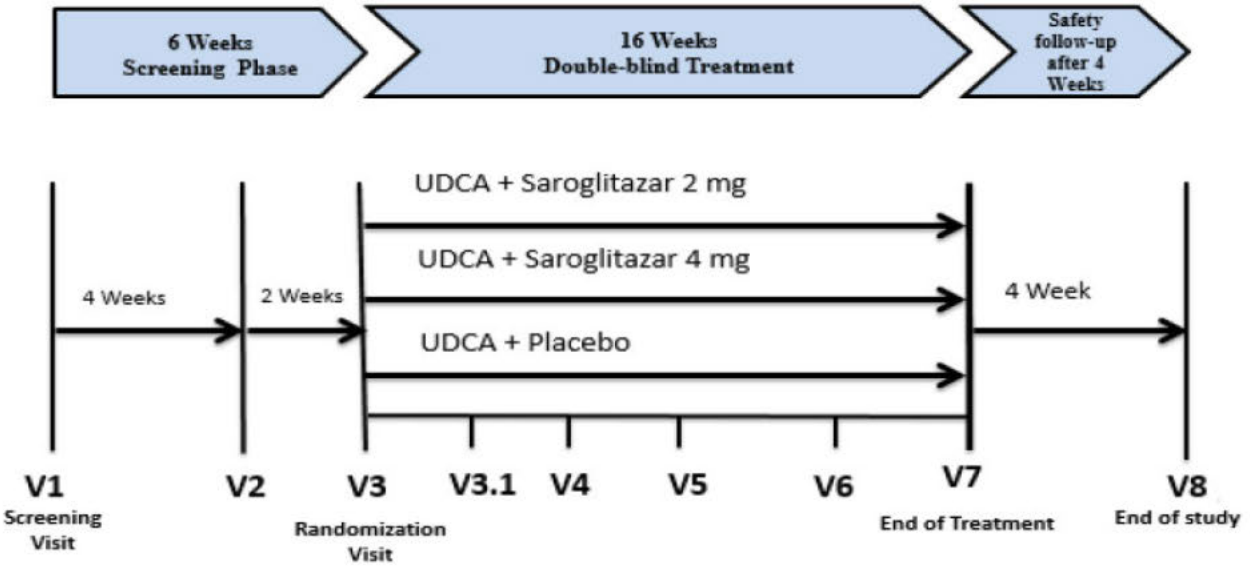
2.2 Study Description

2.2.1 Study design

This is a Phase 2 prospective, multicenter, randomized, double-blind, placebo-controlled study in subjects diagnosed with PBC meeting pre-specified inclusion/exclusion criteria. Male and female subjects aged 18 to 75 years of old will be enrolled in this study. Approximately 36 subjects who meet the inclusion and exclusion criteria will be randomized in a 1:1:1 ratio to have 12 subjects in each arm i.e., Saroglitazar magnesium 2 mg, Saroglitazar 4mg and placebo respectively.

A total of 18 subjects, six subjects in each treatment group are planned for pharmacokinetic assessment. Additional subjects may be enrolled into the study to ensure the pharmacokinetic assessment is performed on at least 6 completed subjects in each treatment group.

This 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, 4 weeks after the treatment phase. The study plan is provided below.



2.2.2 Study plan

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2.3 Randomization

An independent statistician will generate the randomization schedule(s) for study treatment assignment. Eligible subjects will be randomized in a 1:1:1 ratio to receive Saroglitazar magnesium 2 mg, Saroglitazar magnesium 4 mg or placebo, respectively. Block randomization will be performed. The randomization schedule will be generated to ensure the treatment balance by using SAS® software (Version: 9.4 or higher; SAS Institute Inc., USA).

2.4 Blinding and Unblinding

This study is double-blinded. The subjects, investigators and all members of the Clinical Study Team will be blinded to treatment assignments while the study is in progress except the personal involved in the interim analysis. Once the 24th active randomized subject has completed the study (Week 20 visit assessment), an interim analysis will be performed with an unmasking of specified Zydus individuals (Study Director and Lead PI) who are not involved in the conduct of the trial. 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 final database lock has occurred.

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 subjects and to maintain adequate blinding of evaluators.

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

2.5 Interim Analysis

An interim analysis will be conducted when approximately 24th active randomized subject has completed the study, that is Week 20 visit assessment. The purpose of this interim analysis is to assess the further development of Saroglitazar Magnesium in PBC patients and to choose the optimal dose for planning the phase III study. This analysis will evaluate the efficacy based

on liver biochemistries and lipid profiles and will summarize patient demographics and adverse events. No subject level data listing will be generated.

To ensure the integrity of the study data and compliance with the protocol, unmasking of the study is restricted to selected individuals at Zydus as specified in section 2.4. None of the individuals performing the analyses or the individuals informed of the outcome are part of the study team and from the specific time point of unmasking, none of them will be involved in the study conduct related decision making.

3. ANALYSIS POPULATIONS

Subject evaluability and their impact on analysis populations will be determined prior to breaking the blind treatment assignment code and locking the database.

3.1 Efficacy Analysis Populations

The modified intent-to-treat (MITT) population includes all randomized subjects who received at least one dose of study drug and have at least one post-randomized efficacy assessment. The MITT population will serve as the primary population for all efficacy analyses. Last observation carried forward (LOCF) method will be used as an imputation method for the efficacy variables for MITT analysis.

The supportive analysis of the primary and secondary efficacy endpoints will be conducted using the per-protocol population (PP). The PP population includes all randomized subjects who meet all the inclusions and exclusion criteria, completed the treatment phase and have not deviated from or violated the protocol in such a way that could affect the primary efficacy outcome.

The number of subjects excluded from MITT and PP populations and a listing of excluded subjects from each analysis population with reason for exclusion will be presented. Any inconsistencies in key study results between MITT and PP populations will be examined and discussed in the study report. All efficacy analysis will be conducted according to randomized treatment assignment.

3.2 Safety Analysis Population

The safety population includes the subjects who are randomized and received at least single dose of study medication. For safety analyses, subjects will be analyzed according to the actual treatment received.

3.3 Pharmacokinetic Analysis Population

The pharmacokinetic analysis population includes all randomized subjects who have at least one plasma sample collected following exposure to the study drug and have no known specimen collection or analytical deviations which would affect the integrity of the data.

4. SAMPLE SIZE AND POWER CALCULATIONS

This proof of concept study will include a total 36 subjects. No formal sample estimation was done. 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%.

5. SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

Disposition of Subjects

Subject disposition table will be based on all enrolled subjects who are consented to participate in the study. The following summaries will be included in the disposition table: total number of subjects screened in the study, number of subjects who failed screening, number of subjects who were randomized, number of subjects received treatment, number of subjects who completed the study, and number and percentage of subjects who discontinued from the study with reason for discontinuation. Percentages will be based on the number of patients who are randomized. This tabulation will be done overall as well as by treatment. In addition, the number of subjects included in each analysis population (MITT, PP, Safety, PK) will be presented separately.

Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized based on the MITT, PP and Safety populations.

Descriptive summaries will be provided for the demographic and baseline characteristics. Demographic characteristics such as age, gender, race, ethnicity, AST, ALT, ALP, total bilirubin (TB), INR, ECG, vitals, height and weight will be summarized and tabulated by treatment for all the analysis populations. All the continuous variables (i.e., age, height etc.)

will be summarized by n, mean, standard deviation, minimum, median and maximum values. All the categorical variables (i.e., gender) will be summarized as counts and percentages.

Chi-square test will be used to compare the differences in categorical variables between the treatment groups and the one-way analysis variance will be used for the continuous variables.

The average of two assessments (Visit 1 and Visit 2) of liver biochemistries and INR will be considered as baseline values. In case of missing value at any one of the visits, the available value will be considered as baseline.

Medical history, previous and concomitant therapies

Previous therapies are the therapies/medications with stop date prior to the Baseline visit. Any therapy/medication usage at or post Baseline visit is considered concomitant therapy.

A list of complete medical history, including current and past diseases and their respective treatments will be provided by investigational site and subject number and treatment group.

All the concomitant medications will be listed by investigational site and subject number.

All the concomitant medications taken during the study period will be summarized by treatment group.

A summary will be provided for the number and percent of subjects who had previous therapies/medications and a separate summary of subjects who had concomitant therapy/medications. The summary of medical/disease history will be tabulated using frequency and percentages.

All medications administered during the study will be listed and coded using the World Health Organization (WHO) Drug Reference List (version DDEBSEP16). A listing of all prior and concomitant medications including the reported term, preferred term, Anatomical Therapeutic Chemical (ATC) class, start dates, stop dates and other relevant data will be provided. Concomitant medications include all medications taken on or after the date of the first dose of study drug. Prior medications include all medications taken before the date of the first dose of study drug and discontinued before the first dose of study drug.

6. EFFICACY ANALYSIS STRATEGY

6.1 General Considerations

Categorical variables will be summarized with the frequency and percentage of patients in each category. Continuous variables will be summarized descriptively with the number of subjects, mean, standard deviation, minimum, median and maximum values. Change from baseline will be summarized similarly, but also with standard error. The change from baseline will be calculated as follows:

Change from baseline = Post baseline value – Baseline value

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

Decimal Precision

Unless otherwise noted, means, medians, standard deviations, minimums and maximums will be presented to two decimal places, percentages and confidence intervals will be presented to one decimal places; and p-values will be presented to four decimal places.

Missing Date Procedures

Adverse events with completely missing dates will be considered treatment-emergent. Medications with completely missing end dates will be considered concomitant. Adverse events and medications with partially missing start or end dates will be considered treatment-emergent and concomitant respectively unless the non-missing portion of the dates definitively proves otherwise.

For example, if a subject starts treatment on 20FEB2016, then adverse events with onset dates of FEB2016, 2016, or 05DEC would all be considered treatment-emergent, while onsets dates of 2015 or JAN2016 would not be considered treatment-emergent. Medications starting or ending in FEB2016 or 2016 would be considered concomitant, medications ending in JAN2016 or 2015 would not.

6.2 Efficacy Endpoints

Primary Endpoint:

The primary efficacy endpoint is the change from baseline in alkaline phosphatase (ALP) at Week 16 in Saroglitazar magnesium (2 mg and 4 mg) treatment.

Secondary Endpoints:

The following secondary efficacy endpoints will be evaluated in Saroglitazar magnesium (2 mg and 4 mg) treatment as compared to placebo:

- Change from baseline in ALP at Week 4, Week 8, and Week 12 and Week 16.
- Change from baseline in lipid profile (TG, TC, HDL, LDL and VLDL) at Week 4, Week 8, Week 12 and Week 16.
- 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.
- Change from baseline in 7α-hydroxy-4-cholesten-3-one (C4) at Week 16
- Change from baseline in fibroblast growth factor 19 (FGF 19) at Week 16.
- Proportion of subjects with ALP improvement of 15%, 20%, 30%, 40% and normalization at Week 8 and Week 16.
- Change from baseline in QoL at Week 16 by using PBC-40.
- Safety and tolerability of Saroglitazar magnesium 2 mg and 4 mg.
- Pharmacokinetics of Saroglitazar.

6.3 Efficacy Hypotheses

The statistical hypothesis to test the primary efficacy endpoint, change in ALP from baseline to Week 16 for Saroglitazar magnesium 2 mg and Saroglitazar magnesium 4 mg are:

H_o: $\mu s \leq 0$

H1: $\mu s > 0$

Where μs = change from baseline in ALP levels for Saroglitazar magnesium 2 mg or Saroglitazar magnesium 4mg.

6.4 Statistical Methods for Efficacy Analyses

The primary efficacy endpoint, change from baseline in ALP value at Week 16 will be analyzed separately for Saroglitazar magnesium 2 mg and 4 mg using a two-sided paired t-test. The primary analysis will be performed using MITT population with LOCF as imputation method for missing values.

The analysis for the secondary efficacy endpoints, change from baseline in ALP at Week 4, Week 8, Week 12 and week 16, change from baseline in lipid profile (TG, TC, HDL, LDL, and VLDL), liver biochemistries (GGT, ALT, AST, bilirubin and albumin), serum total bile acids, 7α-

hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF 19) and change from baseline in QoL (PBC40) total scores will be analyzed using ANCOVA (Analysis of covariance) model using baseline values and treatment as factors. The p-value for the treatment comparison, estimate of LSMEANS treatment difference (Saroglitazar magnesium (2 mg and 4 mg) – Placebo), and the 95% confidence interval of the LSMEANS difference will be generated from ANCOVA model. Observed and change from baseline values will be summarized descriptively at each visit for all secondary efficacy endpoints.

Frequency and percentage of subjects with ALP improvement of 15%, 20%, 30%, 40% and normalization (achieving abnormal to normal values) at Week 8 and Week 16 will be presented. Difference between the treatment groups will be presented using 95% exact confidence Interval for proportion.

For the PBC40 questionnaire responses, descriptive summaries will be provided for the total and also for each dimensional score.

6.5 Sensitivity Analysis

A sensitivity analysis to explore the robustness of the efficacy results with respect to the protocol deviations will be performed using Per-Protocol population for all efficacy endpoints.

6.6 Subgroup Analyses and Effect of Baseline Factors

Due to the small sample size, no subgroup analysis is planned for this study.

6.7 Multiplicity Strategy

This is the proof of concept study and hence no multiplicity adjustments are planned.

6.8 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. Subjects are required to have at least one post-treatment assessment to be included in the MITT population. Last Observation Carried Forward (LOCF) will be used for the imputation of missing values. Baseline values will not be carried forward for the imputation of missing values. Subjects discontinued from study will be excluded from the PP population.

7. ANALYSIS OF PHARMACOKINETIC ENDPOINTS

Blood samples for pharmacokinetic analysis will be collected on Visits 3, 4, 5, 6 and 7. Samples on Visit 3 and Visit 7 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 24.0 hours post-dose. Only pre-dose (0.0) samples will be collected on Visit 4, Visit 5 and Visit 6. The following PK endpoints will be derived from the plasma concentration-time data for each subject using Phoenix® WinNonlin® professional software (Version 6.4 or higher) provided there are sufficient data available to estimate each PK parameter:

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

- Peak Plasma concentration (Cmax)
- Time to reach peak Plasma concentration (Tmax)
- Area under Plasma concentration vs. time curve till the last time point (AUCt)
- Area under Plasma concentration vs. time curve extrapolated to the infinity (AUCi) after first dose
- Area under plasma concentration vs. time curve in a 24 h dosing interval (AUCtau) after first dose
- Elimination rate constant (Kel)
- Elimination half-life (t1/2)
- Apparent Volume of distribution (Vd/F)
- Apparent Clearance (CL/F)

For Multiple Dose (i.e. for Visit 7)

- Peak Plasma concentration (Cmax,ss)
- Time to reach peak Plasma concentration (Tmax,ss)
- Area under Plasma concentration vs. time curve till the last time point (AUCt)
- Area under plasma concentration vs. time curve in a 24 h dosing interval (AUCtau) after last dose
- Elimination rate constant (Kel,ss)
- Elimination half-life (t1/2,ss)
- Apparent Volume of distribution (Vd/F,ss)
- Apparent Clearance (CL/F,ss)
- Minimal or Trough plasma concentration (Cmin)
- Fluctuation index.
- Accumulation index calculated as a ratio of AUCtau (last dose)/AUCtau (first dose)

No value of Kel and related PK parameters will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile for single or multiple dose PK parameters. All concentration values Below Limit of Quantitation (BLQ) will be set to zero before pharmacokinetic analysis. If the pre-dose concentration appears to be >5% of the Cmax in any subject on Visit 3 (for single dose only), then the descriptive statistics will be presented including and excluding that subject's data.

The AUC values will be calculated using the linear trapezoidal method. Actual sampling times of individual subjects will be used in the PK analysis.

Descriptive summaries for plasma concentration (n, mean, standard deviation, median, minimum, maximum, geometric mean and coefficient of variation) will be presented by sample collection time points and by treatment group.

Line plots (Linear and semi-log) of the mean concentration versus time curves for each treatment from each of the Visit 3 and Visit 7 post dose plasma collections will be plotted. Individual graphs for each treatment will also be presented.

Descriptive statistics (n, mean, standard deviation, median, minimum, maximum geometric mean and coefficient of variation) will be used to summarize the estimated pharmacokinetic parameters at Visit 3 and Visit 7 by treatment group.

8. SAFETY ANALYSIS STRATEGY

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis.

8.1 Safety Endpoints

The safety endpoints are:

- Adverse events.
- Vital Signs (Systolic BP, diastolic BP, pulse rate, oral temperature and respiratory rate)
- Clinical laboratory testing (hematology, clinical chemistry and urinalysis)
- Twelve-lead electrocardiogram (ECG)
- Physical Examination.

8.2 Safety Hypothesis

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of the safety endpoints listed in Section 6.1.

8.3 Statistical Methods for Safety Analysis

Except otherwise stated, the analysis set for all safety analysis is the safety analysis set as defined in Section 2.2. Unless otherwise specified, all safety parameters will be summarized by treatment group by visit.

8.3.1 Extent of Exposure

Study duration is defined as the date of last visit minus the date of the baseline visit plus one. Treatment duration is defined as "the date of last treatment minus the date of the first treatment plus one. If the date of late application is not available, the date of the last visit during the treatment will be used in calculation. If the date of first treatment is not available, the date of baseline visit will be used in calculation. Study duration and the treatment duration will be summarized descriptively.

8.3.2 Adverse Events

The applicable definition of an Adverse Event (AE) is in the study protocol. All AEs occurring from when a patient signs informed consent to when a patient exits the study will be accounted for in the reporting. Analysis and presentation of AEs occurring during the screening period will be separated from those occurring during the investigational period where a comparative evaluation of treatment-emergent AEs is intended. A treatment-emergent AE is an event not present prior to exposure to investigational product or any pre-existing event that worsens following exposure to investigational product. The period for treatment-emergent AE analysis starts from the first exposure to the investigational product until the patient exits the study.

Descriptive summaries (frequencies and percentages) for specific AEs will be presented by system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA Version 19.1) dictionary by treatment group and overall. In addition to an overall presentation of all AEs, reports will be generated for special classes of AEs such as investigational product related AEs, serious AEs, Maximum severity and AEs resulting in treatment discontinuation by treatment group. These reports will be supported by individual patient listings, as necessary.

Adverse events will be counted by the number of events as well as the number of subjects. For the summaries which count the number of patients by treatment group and overall, multiple AEs with the same MedDRA preferred term within the same patient will only be counted once.

Descriptive summaries (frequencies and percentages) for number of subjects experiencing AEs will also be presented.

Only patient listings will be provided for AEs that occur after signing informed consent but prior to exposure to investigational product. These listings will comprise all events occurring during this period in any patient who consented to participate in the study.

These listings will at least contain but not limited to information such as onset and resolution times, maximum severity, causal relationship to study treatment and action taken.

8.3.3 Vital Signs

Descriptive summaries (N, mean, median, standard deviation, minimum and maximum values) of observed values and change from baseline in each vital sign parameter at each assessment visit will be presented. A listing will be provided for the vital signs parameter assessments.

8.3.4 Physical Examination

Physical examination results (normal/abnormal/not done) from scheduled visits will be summarized for each body system.

8.3.5 Laboratory Results

Laboratory values will be presented using the International System of Units (SI units). Clinical laboratory evaluations consist of hematology, clinical biochemistry and urinalysis. Observed and changes from baseline values will be summarized descriptively (N, mean, median, standard deviation, minimum, and maximum values) at each assessment. A summary table of the categorical grade shift changes using the normal ranges from baseline to last study visit will be provided.

For summary purposes, laboratory values that are listed as above or below particular thresholds will be numerically listed as above or below that threshold, respectively, by the minimum measured amount for that parameter. For example, if a parameter is measured to two decimal places, and has a result of "> 6" then, for summary purposes, the value of 6.01

will be used. Values with "<" or ">" will be classified as Low or High, respectively, unless such classifications aren't applicable for that parameter, in which case they will be classified as Normal.

A listing will be provided which contains data for each laboratory parameter. In addition, a listing of all clinically significant abnormal values will be provided.

8.3.6 ECG

A 12-lead electrocardiogram (ECG) was performed at Screening, Baseline, Week 16 and safety follow-up visit at Week 20. ECG results (normal, abnormal clinically insignificant, abnormal clinically significant) will be summarized. Listing of the patient who had gone through the ECG examination will be presented.

9. REFERENCES

Not applicable

10. LIST OF ABBEVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
C4	7α-hydroxy-4-cholesten-3-one
CI	Confidence interval
CL/F	Apparent Clearance
Cmax	Maximum plasma concentration
ECG	Electrocardiogram
FGF 19	Fibroblast growth factor 19
GGT	Gamma glutamyltransferase
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonization
IP	Investigational product
INR	International Normalized Ratio
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-treat
PBC	Primary Biliary Cholangitis
PK	Pharmacokinetic
PP	Per-protocol
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
Tmax	Time to reach peak Plasma concentration
t1/2	Elimination half-life
TB	Total bilirubin
TC	Total cholesterol
TG	Triglyceride-cholesterol
Vd/F	Apparent Volume of distribution
VLDL	Very low-density lipoprotein
WHO	World Health Organization