OBETICHOLIC ACID (OCA) AND BEZAFIBRATE (BZF)

Protocol 977-311

A Phase 3, Open-Label, Long-Term Safety Extension Study Evaluating the Safety and Tolerability of the Fixed-Dose Combination of Obeticholic Acid and Bezafibrate in Subjects with Primary Biliary Cholangitis

Statistical Analysis Plan

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APPROVAL

Upon review of this document, including table and listing shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESIs	Adverse Events of Special Interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BZF	bezafibrate
[redacted]	
CK	creatine kinase
CP	Child-Pugh
CPS	Child-Pugh score
CS	clinically significant
CSR	clinical study report
DB	double-blind
DMC	Data Monitoring Committee
DOB	date of birth
eCRF	electronic case report form
ECG	electrocardiogram
ELF	enhanced liver fibrosis
Fib4	Fibrosis-4
[redacted]	
GGT	gamma-glutamyl transferase
ICH	International Conference on Harmonisation
INR	international normalized ratio
IR	immediate-release
ITT	Intent-to-Treat
IWRS	interactive web response system
KM	Kaplan-Meier

Abbreviation or Specialist Term	Explanation
LTSE	long term safety extension
LS	least-square
MELD	Model for End Stage Liver Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MRS	Mayo Risk Score
MMRM	mixed-effect repeated measures model
Na	sodium
NCS	not clinically significant
[redacted]	
OCA	obeticholic acid
OPTN	Organ Procurement and Transplantation Network
PBC	primary biliary cholangitis
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SI	standard international unit
SMQ	Standardized MedDRA Query
SOC	system organ classes
TE	transient elastography
TEAE	treatment-emergent adverse event
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

1. SCOPE

This statistical analysis plan (SAP) describes the statistical analyses and data presentations planned for protocol 977-311. It provides a detailed description of the strategies, rationales, and statistical techniques to be used to meet the study objectives and additional details to the statistical analyses that were described in the protocol. This SAP will be finalized and signed off before the database lock. Any deviations from the methods specified in this SAP will be documented in the clinical study report (CSR). If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post-hoc in the CSR.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to assess the long-term safety and tolerability of the Obeticholic Acid (OCA) + Bezafibrate (BZF) Full Dose Combination (FDC) tablet in subjects with Primary Biliary Cholangitis (PBC).

2.1.2. Efficacy Objectives

The efficacy objective is to assess the effects of the OCA + BZF FDC tablet in subjects with PBC on the following:

- Biochemical disease markers, including ALP, GGT, ALT, AST, and total and conjugated bilirubin
- ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline
- Noninvasive assessments of liver fibrosis (transient elastography [TE], enhanced liver fibrosis [ELF] score)
- Disease severity scores (GLOBE, UK-PBC, and model of end-stage liver disease [MELD])

2.1.3. Exploratory Objectives

[redacted]

– MELD score ≥15

[redacted]

2.2. Hypotheses

There is no hypothesis in this study.

3. SUMMARY OF STUDY DESIGN

3.1. Overall Study Design

This Phase 3, open-label, LTSE study will evaluate the safety, tolerability, and efficacy of the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) in approximately 133 subjects with PBC for up to 60 months (5 years).

- For subjects from Study 747-213 or Study 747-214 who continue to meet that protocol's requirements, they will transition into Study 977-311 once the study is active at their respective sites. The time subjects have spent in the LTSE phases in

their respective studies, 747-213 or 747-214, will not count toward the 60 months in Study 977-311.

- Eligible subjects from other Sponsor studies may also transition to Study 977-311.

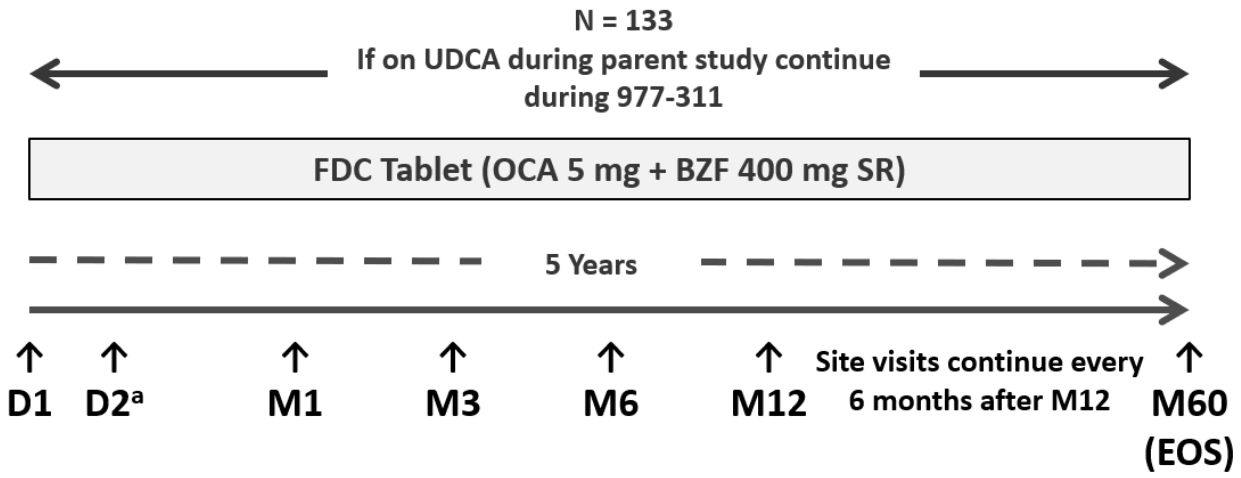
All subjects will transition in Study 977-311 to the OCA + BZF FDC tablet (OCA 5 mg + BZF 400 mg SR) and will receive investigational product once daily at the same time (AM dosing is preferred to align with all study visits) starting on Day 2. All subjects should continue their pre-study dose of UDCA throughout study participation.

After Day 1, Day 2, Month 1, Month 3, Month 6, and Month 12 visits, subsequent in-clinic study visits will occur every 6 months for the assessment of safety, tolerability, efficacy, PK, and PD.

The study design diagram is presented in Figure 1: Study Design Schematic.

3.2. Study Design Diagram

Figure 1: Study Design Schematic



BZF=bezafibrate; D=day; EOS=end of study; FDC=fixed-dose combination; IP=investigational product; LTSE=long-term safety extension; M=month; OCA=obeticholic acid; SR=sustained release; UDCA=ursodeoxycholic acid

Notes: Subjects taking UDCA at the time of enrollment will remain on their stable dose of UDCA during the study. Subjects will be re-consented.

Subjects in either Study 747-213 or Study 747-214 may already be in LTSE. The time subjects spent on LTSE on either study will not be carried over into this study, 977-311. Subjects will spend a total of 60 months (5 years) in Study 977-311.

[a] The Day 2 Visit can be either a virtual or onsite visit. It will be scheduled on Day 2 to Day 7 of the study depending on when laboratory results are available and reviewed. Subjects can elect to pick up IP onsite (onsite Day 2 visit) or have it shipped directly to them (virtual Day 2 visit). For subjects that have IP shipped, the Day 2 virtual visit should be scheduled once the subject receives IP.

3.3. Randomization and Blinding

There are no treatment groups, as this is a single-arm study. Blinding is not applicable to this single-arm study.

3.4. Sample Size Determination

The sample size in this study is not calculated based on statistical consideration.

4. ANALYSIS POPULATIONS AND APPROACHES TO ANALYSIS

4.1. The LTSE Population

The LTSE Population will include all subjects who receive at least 1 dose of the FDC tablet.

4.2. The Pharmacokinetic (PK) Population

The PK Population will include all subjects in LTSE population who receive the FDC tablet and have a PK sample(s) without any major protocol deviations that could potentially affect plasma exposure.

4.3. The Pharmacodynamic (PD) Population

The PD Population will include all subjects with a baseline assessment and at least 1 on-treatment assessment without any major protocol deviations that could potentially affect results.

5. GENERAL CONSIDERATION

Individual subject data obtained from electronic case report forms (eCRFs), central and local laboratories, external sources, and any derived data will be presented in data listings by subject. All data listings that contain an evaluation date will contain a relative study day. Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of investigational product which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of investigational product is designated with an “L” (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc.

Tabulations will be produced for appropriate demographic, Baseline, efficacy, and safety parameters.

For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented. Percentage calculations will be based on non-missing data, unless otherwise specified. Percentages are rounded to 1 decimal place, unless otherwise specified.

For continuous variables, the number of subjects, mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows: mean and median to 1 more

decimal place than the raw data, and SD and SEM to 2 decimal places more than the raw data. In general, the decimal places should not exceed 3 decimal places unless appropriate.

5.1. Baseline Definitions

The Baseline value for statistical analyses is defined as the last evaluations prior to the first administration of investigational product in Study 977-311, unless otherwise specified. For subjects under protocol amendment 2, the baseline value is defined as the evaluations on Day 1.

5.2. Partial Dates

If only a partial date is available and is required for calculation, the following standards will be applied:

- Diagnostic Date (e.g., PBC diagnostic date)
  - For missing day only – Day will be imputed as the first day of the month (i.e., 1).
  - For missing day and month – Day and month will be imputed as the first day of the year (i.e., 1 January).
- Start Dates (e.g., event date, AE onset date, or start date of medication)
  - For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - For missing start day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
  - Imputed start dates must be prior to the stop date. Otherwise, the start date will be further imputed to be the same as the stop date.
- Stop Dates (e.g., AE resolution date or stop date of medication)
  - For missing stop day only – Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
  - For missing stop day and month – Day and month will be imputed as the last day of the year (i.e., 31 December).
  - Imputed stop dates must be on or after the start date. Otherwise, the stop date will be further imputed to be the same as the start date.

5.3. Data Conventions

The precision of original measurements will be maintained in summaries, when possible.

For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, when rounding to the nearest integer, values ≥XX.5 will be rounded up to XX+1 (e.g., 97.5 will round up to 98), while values <XX.5 will be rounded down to XX (e.g., 97.4 will round down to 97).

Percentages based on frequency counts will be based on available data, and denominators will generally exclude missing values, unless otherwise stated. For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Percentages based on frequency counts will be presented as a whole number (no decimal places), and values less than 1% will be presented as "<1%." Values less than 100% but that round up from 99.5% to 100% will be presented as ">99%."

Quantitative laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purposes, the following imputations will be done within the analysis datasets:

For laboratory test results that are below the quantifiable limit:

Imputed laboratory results= (numeric portion of the result) x 0.9

For laboratory test results that are above the quantifiable limit:

Imputed laboratory results= (numeric portion of the result) x 1.1

Standard Quantitative laboratory tests containing less than (<) and greater than (>) symbols are test results that are below and above quantifiable limits, respectively. In order to retain these values for analysis purposes, the following imputations will be done within the analysis datasets:

For laboratory test results that are below the quantifiable limit:

Imputed laboratory results= (numeric portion of the result) x 0.9

For laboratory test results that are above the quantifiable limit:

Imputed laboratory results= (numeric portion of the result) x 1.1

5.4. Calculations

Variables requiring calculation will be derived using the following formulas:

- Days – A duration expressed in days between one date (*date1*) and another later date (*date2*) will be calculated using the following formulas:

  duration in days= date2 – date1 + 1, where date1 ≥first dose date

  duration in days= date2 – date1, where date1 <first dose date

- Months – A duration expressed in months is calculated as the number of days divided by 365.25/12 (approximately 30.4)
- Years – A duration expressed in years between one date (*date1*) and another date (*date2*) is calculated using the following formulas:

duration in years= (date2 – date1 + 1)/365.25, where date1 ≥first dose date

duration in years= (date2 – date1)/365.25, where date1<first dose date

- Age of diagnosis – Age of diagnosis is calculated as the number of years from the imputed year of birth (*DOB*) to the year of diagnosis. The imputed year of birth is derived as year of inform consent – age. The following formula is used:

  age (years)= year of diagnosis – imputed year of DOB + 1

- Height – Height entries made in inches are converted to centimeters using the following formula:

  height (cm)= height (in) × 2.54

- Weight – Weight entries made in pounds are converted to kilograms using the following formula:

  weight (kg)= weight (lb) / 2.2046

- Temperature – Temperature entries in degrees Fahrenheit are converted to degrees Celsius using the following formula:

  temp (degrees Celsius) =5 / 9 × (temp [degrees Fahrenheit] – 32)

- Body Mass Index (BMI) – BMI is calculated using height (cm) and weight (kg) using the following formula:

  BMI (kg/m^2) =weight (kg) / ([height (cm)/100]^2)

- Change from Baseline – Change from Baseline will be calculated as:

  Change=post Baseline value – Baseline value

- Percentage change from Baseline – Percentage change from Baseline will be calculated as:

  Percentage change from Baseline= ([post Baseline value – Baseline value] / Baseline value) × 100

[redacted]

Note: TRANS= ALT ratio to upper limit. When ALT is missing, TRANS=AST ratio to upper limit.

5.5. Analysis Windows

Analysis windows will not be defined in this study. Only the scheduled visits will be included in the analyses. All visits, including unscheduled visits, will be presented in the listings.

6. SUBJECT DISPOSITION

Subject disposition will be tabulated in overall and will include, as appropriate, the following number and proportion of subjects:

- LTSE population
- PK population
- Completed study
- Study discontinuation and reasons
- Investigational product discontinuation and reasons

Disposition summaries of both end of study and end of treatment will be presented for each analysis population and will be tabulated in overall.

A by-subject data listing of study completion information including the reason for premature treatment and study withdrawal, if applicable, will be presented.

6.1. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any significant way without proper notification to the Sponsor (or designee).

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database. Major protocol deviations will be summarized by deviation category using the LTSE population.

Protocol deviations will be presented in a by-subject data listing.

7. DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

7.1. Demographics and Baseline Characteristics

Demographic variables will include the following:

- Age at informed consent (Continuous and Categorical (<65 and ≥65))
- Sex (Male and Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)
- Geographic Region

Other Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

Key liver function test results as a continuous variable and categorized as follows:

- ALP (U/L)
- Total Bilirubin (μmol/L)
- Albumin (g/L)
- Use of UDCA (Yes/No)

- Total daily dose of UDCA (mg) as determined using the last dosage reported prior to the first dose

Demographics and Baseline characteristics will be summarized and presented in overall for LTSE and PK populations. For categorical variables, the number and percentage of subjects within each category, including a category for missing data, will be presented. For continuous variables, summary statistics will include the number of subjects and the mean, SD, SEM, median, 25th and 75th quartiles, minimum, and maximum values. No inferential statistical comparisons will be performed.

All demographic and Baseline characteristics data will be presented in by-subject data listings.

7.2. Baseline PBC Disease Characteristics

Baseline PBC disease characteristics will be summarized using data collected from the PBC Disease History and other eCRFs. Variables of the PBC Disease History include the following:

- Age at PBC diagnosis
- Duration of PBC in years at time of informed consent
- History of PBC related pruritus (Yes/No)
- Severity of most recent pruritus event
  - Ongoing at screening
- History of PBC-related fatigue (Yes/No)
  - Ongoing at screening
- Overall severity of PBC-related fatigue

Baseline PBC disease characteristics will be summarized and presented in overall for LTSE population.

Baseline PBC disease characteristics will be presented in by-subject data listings.

8. MEDICAL HISTORY

Verbatim terms on eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA).

Medical history will be summarized by system organ class, preferred term using the LTSE population. Summaries will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

Medical history will be presented in a by-subject data listing.

9. EFFICACY ANALYSES

The efficacy endpoints of the study are defined below. Additionally, the planned analyses for these endpoints are described. All efficacy endpoints will be presented in by-subject data listings.

Missing data will be assumed to be missing at random. In order to determine the effect of missing data on the analysis, efficacy endpoints will be analyzed using different methods of imputation as described below.

During the conduct of the study, the DMC may recommend refining the missing data strategy to better address the observed pattern of missing data, based on blinded monitoring of the data.

All efficacy analyses will be summarized using descriptive statistics at Baseline and at each scheduled postbaseline visit. The change from baseline and percent change from baseline will also be summarized. Descriptive statistics, including change from baseline, percent change from baseline, and estimates of least-square (LS) means, SEs, and 95% CIs, will be presented. Estimates of the mean difference between treatment groups, the SE of the difference, and 2-sided 95% CI of the difference will also be presented.

In efficacy analyses, subjects who do not provide an assessment at the specified timepoint for the defining of response will not be included. That is, for the percentage of responders, the subject will not be included in the numerator or the denominator.

9.1. Efficacy Endpoints

The LTSE Population will be the population used for the efficacy analyses. Baseline is defined as the last assessment performed before the first dose of investigational product in Study 977-311, unless otherwise specified.

The efficacy endpoint at post-baseline site visits includes:

- Response rate of ≥40% reduction from baseline and normalization rates of ALP
- Normalization rates of GGT, ALT, AST, total and conjugated bilirubin
- Change from baseline in GGT, ALT, ALP, AST, and total and conjugated bilirubin
- Percentage of subjects with ALP <1.67x ULN, total bilirubin ≤ULN, and ALP decrease of ≥15% from baseline
- Change from baseline in noninvasive markers of liver fibrosis, including liver stiffness measured by TE and ELF score
- Change from baseline in the GLOBE, UK-PBC, and MELD scores

All continuous and categorical additional endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit. No statistical inference will be done on those endpoints.

The intercurrent event in this study includes the use of prohibited medication and treatment discontinuation. Data collected after the intercurrent events, such as the use of prohibited medications, and data collected after treatment discontinuation will be included in the analyses (Treatment Policy Estimand).

The 5 attributes of the efficacy estimand are provided in Table 1.

Table 1: Attributes of Efficacy Estimand

Estimand Attribute	Elements
Population	All subjects with PBC who participated and are actively taking investigational product in Study 747-213 or Study 747-214 (or other Sponsor studies)
Treatment	OCA+BZF FDC Tablets
Efficacy Endpoint	All efficacy endpoints
Intercurrent Events	Use of Prohibited medication (Treatment Policy) Treatment Discontinuation (Treatment Policy)
Primary Efficacy Endpoint Population Level Summary	Descriptive summary in the target population

9.2. Exploratory Endpoints

[redacted]

– MELD score ≥15

[redacted]

- Time to first occurrence of each individual component of the composite event endpoint.

All continuous and categorical additional efficacy endpoints will be summarized using descriptive statistics at baseline and at each scheduled post-baseline visit. No statistical inference will be done on those endpoints.

Kaplan-Meier (KM) estimates will be calculated for all time to event endpoints. The quartiles, including the median time-to-event and their respective 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve".

For the additional endpoints, data collected after the intercurrent events, such as the use of prohibited medications, and data collected after treatment discontinuation will be included.

9.2.1.1. Child-Pugh

The Child-Pugh score (CPS) is calculated within EDC by adding the scores of the 5 factors and can range from 5-15. Child-Pugh class is either A (a score of 5-6), B (7-9), or C (10 or above). Each of the factors is outlined in Table 2.

Table 2: Child-Pugh Score

Factor	Units	Points		
		1	2	3
Serum bilirubin	µmol/L	<34	34-50	>50
	mg/dL	<2.0	2.0-3.0	>3.0
Serum albumin	g/L	>35	35-28	<28
	g/dL	>3.5	3.5-2.8	<2.8
Prothrombin time	Seconds prolonged	0-3	4-6	>6
	INR	<1.7	1.7-2.3	>2.3
Ascites		None	Mild	Moderate-Severe
Hepatic encephalopathy		No	Grade 1 or 2	Grade 3 or 4

The ascites and hepatic encephalopathy variables are based on the investigator's clinical assessment.

The CP score will be summarized in the same manner as described above for the MELD score.

Child-Pugh class will be presented in shift tables showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of subjects within each shift classification.

Individual factors will be presented in a listing.

9.3. Interim Analyses and Data Monitoring Committee

9.3.1. Interim Analyses

There is no interim analysis in this study.

9.3.2. Data Monitoring Committee

An independent DMC will review safety and efficacy data from this study for their recommendation. Ad hoc meetings will be convened, as appropriate. The role and scope of the DMC will be further described in a separate charter.

9.4. Multiple Comparisons/Multiplicity

No adjustment on type I error will be performed in this study.

9.5. Subgroup Analyses of Efficacy

No subgroup analysis of efficacy is planned in this study.

10. SAFETY ANALYSES

Safety analyses will be performed using the LTSE population. No inferential comparison of safety endpoints will be performed, unless otherwise specified.

10.1. Exposure to Study Treatment

The extent of exposure will be summarized using descriptive statistics.

Duration of exposure (days) to investigational product will be calculated as follows:

- Exposure to investigational product = [(Date of last investigational product dose–Date of 1st investigational product dose) + 1] – Total duration of temporary investigational product discontinuation

The duration of each incidence of temporary investigational product discontinuation will be calculated as follows:

- Duration of temporary discontinuation of investigational product = (Date of restart of investigational product – Date of temporary discontinuation of investigational product) + 1.

The total duration of temporary investigational product discontinuation is the sum duration of temporary discontinuation of investigational product over each incidence of discontinuation.

Total subject exposure to investigational product will be calculated by adding the doses taken by a subject during the study and will be summarized using descriptive statistics.

A summary of subjects who had an increase in dose and who had a decrease in dose at least once during the study will be provided in terms of frequency count (n) and percentages (%).

Subject's overall compliance (%) with investigational product will be calculated as follows:

- number of tablets consumed during study / number of tablets expected to be consumed during study) *100

where

- number of tablets consumed during study = number of tablets dispensed-number of tablets returned

Subject compliance with investigational product will be summarized using descriptive statistics. Percent compliance will be summarized separately for subjects who completed the study versus those who withdrew early so as to distinguish between those subjects who were compliant throughout the entirety of the study versus those who were compliant until they withdrew from the study.

All exposure data will be presented in a by subject data listing.

10.2. Adverse Events

AEs are defined as any untoward medical occurrence associated with the use of the investigational product in humans, whether or not considered related to the investigational product. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with any use of the investigational product, without any judgment about causality and irrespective of route of administration, formulation, or dose, including an overdose.

AEs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using MedDRA dictionary version 22.0. Subjects experiencing the same event more than once will be counted only once at the most severe grade and the closest relationship to study treatment.

10.2.1. Treatment-emergent Adverse Events

An AE is defined as a treatment-emergent adverse event (TEAE) in the DB period if it meets one or more of the following criteria:

- An AE starting on or after the first study drug dose.
- An AE occurring prior to the first study drug dose that worsens (increase in grade) after the first study drug dose during Double-Blind period.
- An AE with a missing start date but with an end date after the first study drug dose date.
- Any AE started later than the 30 days of the last dose of study drug is not counted as a TEAE.

10.2.2. Serious Adverse Events

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Any malignancy is to be reported as a serious AE.

Events **not** considered to be SAEs are hospitalizations for:

- Routine monitoring of the studied indication and not associated with any deterioration in condition or AE
- Elective treatment for a pre-existing condition that did not worsen
- Respite care or observation when there is no AE associated with the hospitalization

10.2.3. TEAE Analyses

All AE summaries will be restricted to TEAEs. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall summary of TEAEs
- Subject incidence of TEAEs and the total number of entries by MedDRA SOC and PT.
- Subject incidence of TEAEs by MedDRA SOC, PT, and highest severity. At each level of subject summarization, a subject is classified according to the highest

severity if the subject reported 1 or more events. AEs with missing severity will be considered severe for this summary.

- Subject incidence of TEAEs by MedDRA SOC, PT, and closest relationship to investigational product (Related/Not Related). Related AEs are those with relationships reported as "Definite," "Probable," or "Possible," and unrelated AEs are those with relationships reported as "Unlikely" or "Not Related." At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and the total number of entries by MedDRA SOC and PT.
- Subject incidence of TEAEs leading to investigational product withdrawal or study discontinuation by MedDRA SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Subject Discontinued from Study" is checked.

The following listings will be presented by subject:

- All adverse events
- Serious adverse events (a subset of the AEs where serious is marked as "Yes").
- Severe adverse events (a subset of AEs where severity is marked as "Severe").
- Related adverse events (a subset of the AEs where relationship marked as "Definite," "Probable," or "Possible").
- Adverse events leading to Study Drug Withdrawal or Study Discontinuation (a subset of the AEs where Action Taken with Study Treatment is checked as "Drug Withdrawn" or where "Subject Discontinued from Study" is checked).
- Adverse events leading to death.

10.2.4. Adverse Events of Special Interest (AESI)

The AESIs include pruritus, hepatic injury, myalgia and renal impairment.

10.2.4.1. Pruritus

Pruritus is both the most common symptom of PBC and was the most frequently reported AE in the Phase 2 PBC studies for OCA. Accordingly, pruritus is considered an AE of special interest.

Treatment-emergent pruritus, defined as any preferred term including "Prur," will be summarized separately by the MedDRA SOC, treatment group, and PT as a subset of all TEAEs. Summaries will include a summary of the crude incidence of Pruritus TEAEs and SAEs by system organ class and preferred terms. Hepatic Injury

Hepatic injury is defined as events included in the Hepatic Disorder Standardized MedDRA query (SMQ), excluding the following sub-SMQs: alcohol related, congenital, familial, neonatal and genetic disorders of the liver; liver infections; and pregnancy-related hepatic injury. Summaries will include a summary of the crude incidence of hepatic disorder TEAEs and SAEsby system organ class and preferred terms.

10.2.4.2. Myalgia

Myalgia is defined as events with the preferred term of myalgia. Summaries will include a summary of the crude incidence of myalgia TEAEs and SAEs by system organ class and preferred terms.

10.2.4.3. Renal Impairment

Renal impairment is defined as events included in the following broad SMQs: acute renal failure, chronic kidney disease, proteinuria, renovascular disorders, or tubulointerstitial diseases.

Summaries will include a summary of the crude incidence of myalgia TEAEs and SAEs by system organ class and preferred terms.

10.3. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in both conventional and standard international system of units using descriptive statistics at Baseline and at each on-study evaluation. Baseline is defined as the mean of all available evaluations prior to the first administration of investigational product.

The normal ranges of the selected lab parameters are defined below. The abnormal indicators of the selected lab parameters will be derived based on these normal ranges (inclusively):

- ALP 44-122 U/L
- ALT 0-45 U/L
- AST 0-45 IU/L
- GGT 0-65 IU/L (male) 0-60 IU/L (female)
- Total Bilirubin 1.71-12.3 umol/L
- Direct Bilirubin 0-0.4 mg/dL
- Cholesterol 0-169 mg/dL (age <=19), 0-199 mg/dL (age >19)
- LDL 0-109 mg/dL (age <=19), 0-99 mg/dL (age >19)
- HDL >39 mg/dL
- Creatinine 0.57-1.27 mg/dL
- Creatine 0.0-0.7 mg/dL (male) 0.1-1.0 mg/dL (female)
- CK 41-439 U/L (male, age 18-50 years old), 41-331 U/L (male, age 51-80 years old),

32-182 (female, age 18-80 years old)

For the other lab parameters, the normal ranges and abnormal indicators are based on the values in the data from the central or local labs.

In addition, shift tables (i.e., low-normal-high at Baseline versus low-normal-high at post-Baseline visit in a 3-by-3 contingency table) from Baseline to worst value, last value, and at each scheduled post Baseline visit will be provided for hematology and serum chemistry to assess changes in laboratory values from Baseline to each on-study evaluation from the central or local labs. The subjects meeting Hy's law criteria (defined as AST or ALT ≥3 xULN together with total bilirubin ≥2 xULN at any timepoint) will be summarized by visit.

Urine chemistry and urinalysis results will not be summarized but will be provided in a data listing.

All clinical laboratory data (including central and local) will be presented in by-subject data listings.

10.4. Vital Signs

The results and change from Baseline to each on-study evaluation visit will be summarized for weight, oral temperature, sitting heart rate, respiratory rate and sitting blood pressure.

All vital sign data will be presented in by-subject data listings.

10.5. Electrocardiograms (ECGs)

Overall interpretation results for electrocardiograms (ECGs) and the investigator interpretation results are collected as normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS). Subjects whose interpretations shift from normal to abnormal (CS or NCS) will be listed separately, including description of the abnormality and any associated comments.

All ECG results will be presented in by-subject data listings.

10.6. Physical Exam

The results of physical exam will be summarized by visit.

All physical exam data will be presented in by-subject data listings.

10.7. Prior and Concomitant Medications

Prior medications are those medications with start and stop prior to the initial dose of investigational product. Concomitant medications are those medications started prior and continued after the initial dose of investigational product were. If it cannot be determined whether the medication was a concomitant medication due to a partial start or stop date or if the medication is taken on the same date as the initial dose of investigational product, then it will be counted as a concomitant medication.

Prior medications will be listed only. Concomitant medications will be summarized by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) class level 2, WHO ATC class level 4 and preferred name using the LTSE Population. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

10.8. Subgroup Analyses of Safety

No subgroup analysis of safety is planned in this study.

11. DEVIATIONS FROM PROTOCOL

There have been no deviations between the protocol-defined statistical analyses and those presented in this statistical analysis plan.

12. REFERENCES

Angeli P, Garcia-Tsao G, Nadim MK, et al. News in pathophysiology, definition and classification of hepatorenal syndrome: A step beyond the International Club of Ascites (ICA) consensus document. Journal of hepatology. 2019 Oct;71(4):811-22.

APPENDIX A. DATA PRESENTATION CONVENTIONS:

Unless otherwise specified, the baseline value for analyses of all parameters is defined as the last non-missing value prior to the first administration of investigational product.

For categorical variables, the number and percentage of subjects within each category of the parameter, including a category for missing data, will be presented. Percentage calculations will be based on the analysis population, unless otherwise specified.

For continuous variables, summary statistics will include the number of subjects and the mean, standard deviation (SD), standard error of the mean (SEM), median, 25^{th} and 75^{th} quartiles, minimum, and maximum values.

All statistical analyses will be performed using SAS statistical software Version 9.4 or higher unless otherwise noted.