OBETICHOLIC ACID (OCA)

747-401

A Phase 4, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Pharmacokinetics and Safety of Obeticholic Acid in Patients with Primary Biliary Cholangitis and Moderate to Severe Hepatic Impairment

Statistical Analysis Plan

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Sponsor

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16.1.9 DOCUMENTATION OF STATISTICAL METHODS

747-401 Statistical Analysis Plan, Version 1.0, dated 27 Sep 2021.

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Statistical Analysis Plan

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR (1)	Autoregressive (1)
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration
BMI	Body mass index
BLQ	Below limit of quantification
BIW	Twice per week
C4	7α-hydroxy-4-cholesten-3-one
CA	Cholic acid
CDCA	Chenodeoxycholic acid
CLDQ	Chronic liver disease questionnaire
CI	Confidence interval
CM	Concomitant medication
CP	Child-Pugh
CV	Coefficient of variation
DB	Double-blind
DBext	Double-blind extension
DCA	Deoxycholic acid
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ELF	Enhanced liver fibrosis
EQ-5D-5L	EuroQol five-dimensional
ET	Early termination
EOT	End of treatment
EOS	End of study
FGF-19	Fibroblast growth factor-19

Abbreviation or Specialist Term	Explanation
FXR	Farnesoid X receptor
GGT	Gamma-glutamyl transferase
HA	Hyaluronic acid
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
INR	International normalized ratio
IP	Investigational product
ITT	Intent-to-treat
IWRS	Interactive web response system
KM	Kaplan-Meier
LCA	Lithocholic acid
LOESS	Locally estimated scatterplot smoothing
LLOQ	Lower limit of quantification
LLN	Lower limit of normal
LS	Least square
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model of end stage liver disease
Min	Minimum
MMRM	Mixed model repeated measures
MR	Metabolite ratio
OCA	Obeticholic acid (also known as INT-747)
PBC	Primary biliary cholangitis (also known as primary biliary cirrhosis)
PD	Pharmacodynamics
PK	Pharmacokinetics
P3NP	procollagen 3 N-terminal peptide
PT	Preferred term
QW	Once per week
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan

Abbreviation or Specialist Term	Explanation
SAS	Statistical analysis system
SD	Standard deviation
SE	Standard error
SI	Standard international
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TE	Transient elastography
TEAE	Treatment-emergent adverse event
TIMP-1	Tissue inhibitor of metalloproteinase
TLF	Table, listing, and figure
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

1. SCOPE

This statistical analysis plan (SAP) describes the statistical analyses and data presentations planned for protocol 747-401, A Phase 4, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Pharmacokinetics and Safety of Obeticholic Acid in Patients with Primary Biliary Cholangitis and Moderate to Severe Hepatic Impairment. 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 prior to 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

- To evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and OCA metabolite glucuronide compared with placebo
- To evaluate the safety and tolerability of OCA treatment compared with placebo

2.1.2. Secondary Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - The MELD score and its components
  - CP score and its components
  - Liver biochemistry including total and direct bilirubin, alkaline phosphatase (ALP), and aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transaminase [GGT]), international normalized ratio (INR), creatinine, albumin, platelets
  - Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids

2.1.3. Exploratory Objectives

- To evaluate the effect of OCA treatment compared to placebo on:
  - Noninvasive markers of liver fibrosis (Enhanced Liver Fibrosis [ELF]™score)
  - Noninvasive measurement of liver stiffness (transient elastography [TE])
- To assess the PK/Pharmacodynamic (PD) relationship of OCA with:
  - PK parameters compared to PD parameters and safety and tolerability assessments

- To assess patient reported outcomes (Pruritus Visual Analogue Scale [VAS], PBC-40, EQ 5D-5L, Chronic Liver Disease Questionnaire [CLDQ]
- To assess clinical events consistent with end-stage liver disease
  - Death (all cause)
  - Liver transplant
  - MELD score ≥15 (for patients with MELD ≤12 at baseline)
  - Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥2), spontaneous bacterial peritonitis
  - Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
  - Hepatocellular carcinoma (HCC)

2.2. Hypotheses

The primary objective of this study is to evaluate the PK of OCA and its conjugates, safety and tolerability of OCA compared with placebo. Therefore, there is no formal statistical hypothesis to be tested.

3. SUMMARY OF STUDY DESIGN

This is a double-blind, randomized, placebo-controlled study evaluating the PK and safety of OCA in patients with PBC and moderate to severe hepatic impairment. It is a Phase 4 study in regions where OCA has received regulatory approval for PBC; in all other regions, this study is considered Phase 3b.

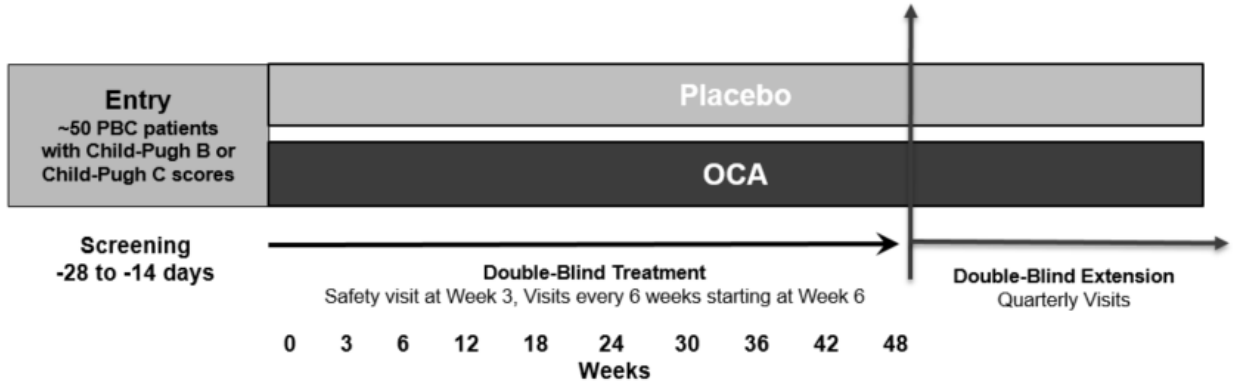
Approximately 50 patients (including at least 20% of patients with CP-C) will be enrolled in the study. Patients will be screened ≥14 days but not more than 28 days prior to entering the study (Day 1). Patients who meet all eligibility requirements will be randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or OCA. Randomization will be stratified by CP class. Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores.

Patients will receive double-blind treatment for at least 48 weeks. During the 48-week treatment period (ie, Day 1 through Week 48), an initial safety visit will occur at Week 3. After the Week 6 Visit, subsequent clinic visits will occur approximately every 6 weeks for the assessment of safety, tolerability, PK, and PD. Titration may be considered as early as the Week 12 Visit. Fasting PK samples (ie, trough only) will be obtained from all patients on Day 1, Week 6, and Week 36 prior to dose administration. Post-dose serial PK assessments (including a trough sample) will be performed in all patients at Weeks 12, 18, 24, 30, and 48.

Patients who have completed their 48-week double-blind treatment period will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked (approximately 3 years).

All patients will initiate investigational product (IP) once weekly with 5 mg OCA or matching placebo. Titration may be considered as early as the Week 12 Visit. Following visit procedures at Week 12, if the IP is tolerated and laboratory assessments do not indicate a safety concern, the patient may up-titrate to OCA 5 mg twice weekly and may start the higher dose regimen no earlier than 2 days after they took their last dose. Dosing will then occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients can be considered for further up titration as described below. At each titration visit, the patient may start the higher dose regimen no earlier than 2 days after the prior dose. Patients may titrate to a maximum dose of OCA 10 mg twice weekly at least 3 days apart.

Figure 1: Study Design



OCA = obeticholic acid, PBC = primary biliary cholangitis

Notes: Initial dose titration of investigational product may be considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may occur no earlier than 6 weeks after the previous dose titration and will be based on tolerability.

Patients who complete Week 48 will continue double-blind treatment until all randomized patients have completed their participation in the 48-week treatment period and the database for that period is locked.

Table 1. Planned OCA or Matching Placebo Dosing Regimen

	Child-Pugh B and Child-Pugh C (Moderate and Severe Hepatic Impairment)	
	Treatment Group	
	OCA	**Placebo**
Starting Dose (Day 1)	5 mg once weekly	matching placebo once weekly
Titration 1[a]	5 mg twice weekly[b]	matching placebo twice weekly[b]
Titration 2[a]	10 mg twice weekly[b]	matching placebo twice weekly[b]

[a] Planned titration regimen is shown; however, the titration of dose and/or frequency is dependent on patient tolerability.

[b] Dosing per the twice weekly schedule must be at least 3 days apart.

3.1. Subject Selection

This study will be conducted at approximately 50 international study sites with experience in treating patients with PBC with moderate to severe hepatic impairment defined as CP-B and CP-C. Prospective patients will be identified primarily from the hospital and/or physician's database of patients with PBC, or may be referred from other physicians. Patients may self-refer to an Investigator if they become aware of the study through local, national, or international PBC patient societies, forums, or networks. Subject Inclusion and Exclusion criteria can be found in Sections 8.2 and 8.3 of the protocol.

3.2. Randomization and Blinding

This study will be conducted in a double-blind, placebo-controlled manner. Enrolled patients who meet all eligibility requirements will be randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or OCA based on a predefined randomization code (generated by Sponsor or designee) using an interactive web response system (IWRS), which the Sponsor intends will serve as a computer-based patient registration system at Screening and Day 1.

Randomization will be stratified by CP class (CP-B or CP-C). Baseline MELD scores will be monitored on an ongoing basis to ensure adequate distribution of MELD scores. The IWRS will serve as the IP inventory and management system and may be integrated with the study database.

The Investigator or designee will be required to register the patient in the IWRS and may be prompted to provide patient data necessary to properly randomize and allocate the patient to treatment. A randomization number will be assigned and IP (placebo or OCA) dispensing information will be provided (eg, bottle numbers allocated) while maintaining the study blind.

The sponsors, patients, investigators, and study site staff will be blinded to the patient's treatment allocation during the patient's participation in the double-blind phase of the study.

Treatment assignment for individual patients will be made available to the Investigator for medical emergency use only (such as unblinding which is necessary in order to treat a serious adverse event through the IWRS system). When possible, the Medical Monitor should be consulted in the event that a medical emergency necessitates unblinding (ie, in situations where knowledge of the blinded treatment assignment is necessary for further medical management of the patient). If it is not reasonable to inform the Medical Monitor in advance of the unblinding, the Investigator must promptly document in the patient's record the rationale for unblinding and should subsequently contact the Medical Monitor to explain any premature unblinding of treatment assignment. Procedures for unblinding a patient's treatment will be provided separately to the Investigator. Similarly, if the Medical Monitor breaks the blind for an individual patient for the purpose of evaluating an emergent safety issue, the Medical Monitor will document within study documentation the rationale, circumstances, and the person or persons being informed about the unblinding.

The data monitoring committee (DMC) will have access to the IWRS and will be able to unblind individual patients. Refer to Section 15.8 of the study protocol for further details regarding DMC access to blinded and unblinded data. The DMC will document details about any unblinded patient data reviews in the closed session DMC minutes, which will be made available

to the Sponsor only after the database is locked and the study is unblinded. Cases of premature unblinding, as noted above, will also be reviewed by the DMC.

Access to treatment assignments will also be made available to the designated Intercept staff responsible for expedited safety reporting of suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities.

3.3. Sample Size Determination

To reasonably characterize the PK of OCA in patients with hepatic impairment, a simulation-based approach estimated a requirement of approximately 20 patients in the OCA treatment group assuming a 15% discontinuation rate. A total of 30 patients is adequate with 10 patients on placebo to be included as a comparator and 20 patients on OCA. An additional 20 patients will be enrolled to support safety and efficacy evaluations. Therefore, approximately 50 patients (including at least 20% of patients with CP-C) will be randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo and OCA.

4. ANALYSIS POPULATIONS AND APPROACHES TO ANALYSIS

4.1. Randomized Population

The Randomized Population will include all randomized patients.

4.2. Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all randomized patients who received any amount of IP (OCA or placebo). The ITT Population will be the primary population used for summarizing efficacy and pharmacodynamic analyses assessments. Subjects will be analyzed according to randomized treatment.

4.3. Safety Population

The Safety Population will include all patients who received at least one dose of IP (placebo or OCA). The Safety Population will be the primary population used for safety analyses. Subjects will be analyzed according to treatment actually received.

4.4. Pharmacokinetic Population

The PK Population will include all patients receiving OCA who have adequate concentration-time profiles to characterize OCA and its conjugates and must not have any major protocol deviations that potentially affect exposure levels.

4.5. Non-COVID-19 Impacted Population

Non-COVID-19 Impacted Population will include all randomized subjects who do not have any COVID-19-related protocol deviations. The Non-COVID-19 Impacted population will be used for sensitivity analyses for the primary and secondary efficacy endpoints.

5. SUBJECT DISPOSITION

Subject disposition will be tabulated by treatment group and overall and will include the number and proportion of subjects:

- Enrolled
- Randomized
- Randomized but not treated
- ITT Population
- Safety Population
- PK Population
- Non-COVID-19 Impacted Population
- Subjects who completed the study, withdrew from the study and the reasons for the withdrawal
- Subjects who completed the study treatment, withdrew from the study treatment and reasons for the withdrawal
- Subjects who completed Week 48 Visit of double-blind (DB) phase
- Subjects' study status post study treatment as recorded on the eCRF.

Proportions will be out of the number of randomized subjects.

Similar disposition summary will be done also other ITT, Safety, PK and Non-COVID-19 impacted population. Proportions will be out of the number of subjects in the given population.

Subjects' completion/discontinuation status will be listed including subject identifier, informed consent date, treatment completion, date of last treatment, dose regimen at date of last treatment, reason for treatment discontinuation, study completion, date of study completion or early withdrawal, and reason for study discontinuation.

5.1. Protocol Deviations

The Investigator is not permitted to deviate from the protocol without proper notification to the Sponsor (or designee). Only the Sponsor may amend the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol amendment to implement the change and obtain regulatory approval. The only exception is when the Investigator considers a patient's safety to be compromised if immediate action is not taken.

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock and unblinding of individual subject treatment information. Major protocol deviations will be summarized by deviation category and treatment group for the ITT Population.

Protocol deviations related to COVID-19 are recorded in the Clinical trial management system as outlined within the Protocol Deviation and Non-Compliance Plan and will also be summarized by deviation category and treatment group.

Protocol deviations will be listed by subjects.

5.2. Inclusion/Exclusion Criteria

Inclusion/exclusion criteria definitions and violations will be listed. If no inclusion/exclusion violations are reported, this will be noted in place of the listing.

6. DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

Demographics and baseline characteristics will be summarized and presented by treatment group and overall for ITT, Safety, and PK Populations.

Age (years), height (cm), weight (kg), body mass index (BMI) (kg/m2), baseline CP score and baseline CP class (Class B/Class C), baseline MELD score, and Rotterdam criteria at baseline will be summarized descriptively. Summary statistics will include the number of subjects and the mean, standard deviation (SD), standard error of the mean (SE), median, 25^{th} and 75^{th} quartiles, minimum, and maximum values. Key liver function test results including ALP, total bilirubin, INR, platelets, albumin, Total daily dose of UDCA (mg) at baseline, Time from first initiated UDCA to first dose (weeks), and Time from last date of highest UDCA use to first dose (weeks) will also summarized descriptively.

Sex, Race, Ethnicity, and Use of UDCA (Yes/No) will be summarized by frequency counts and percentages. A subject can have multiple races and will be summarized as Multiple Races. A subject can also have multiple ethnicities and will be summarized as Multiple Ethnicities.

BMI is calculated based on weight and height at baseline.

Demographic data and baseline characteristics (as detailed above) as well as informed consent data will be listed.

- Age (in years) is derived by IWRS as year of screening minus year of birth
- Height (in cm) = height (in inches) * 2.54
- Weight (in kg) = weight (in lbs) * 0.4536
- BMI (kg/m2) = Weight(kg)/[Height(cm)/100]2
- Total daily dose of UDCA (mg) at baseline is determined as the last dosage reported prior to the first dose.
- Time from first initiated UDCA to first dose (weeks) = (first dose date – date of first initiated UDCA)/7
- Time from last date of highest UDCA use to first dose (weeks) = (first dose date - date of highest UDCA)/7

- Rotterdam criteria (Kuiper 2009) at baseline is defined as:
  - Low = Total Bilirubin< ULN and Albumin>LLN
  - Moderate = Total Bilirubin<ULN and Albumin<LLN or Total Bilirubin>ULN and Albumin>LLN
  - High = Total Bilirubin>ULN and Albumin<LLN

Demographics and baseline characteristics will be listed by subject.

7. PBC DISEASE HISTORY

PBC disease history will be summarized and presented by treatment group and overall for ITT, Safety, and PK Populations. The number and percentage of subjects in each of the following categories will be presented.

- Age at PBC diagnosis
- Duration of PBC in years at time of informed consent
- Time in years from PBC Diagnosis to first dose of UDCA
- History of PBC related pruritus (Yes/No)
- Severity of most recent pruritus event
- Pruritus ongoing at time of screening (Yes/No)

8. PRIOR THERAPY AND MEDICAL HISTORY

Prior therapy and medical history are any therapy, procedures, or diseases that occurred, or any medication taken prior to the first day of study drug dosing or prior to randomization date if subjects were never dosed.

Medical history will be mapped to preferred terms and system organ classes using MedDRA dictionary version 24.0 and summarized by system organ class, preferred term, and treatment group and overall using the Safety population. Summaries will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

A listing of medical history by subject will be provided. A listing of cirrhosis status assessment by subject will also be provided.

Historical procedures will be coded with MedDRA version 24.0. A summary of historical procedures will be presented by MedDRA SOC, PT, and by treatment group and overall using the Safety Population. A listing of historical procedures by subject will be provided.

9. EFFICACY ANALYSES

The efficacy endpoints of the study are defined below. Additionally, the planned analyses for these endpoints are described.

The efficacy analyses are additional endpoint in this study and will be performed on the ITT Population, as defined in Section 4.2. Summary statistics will be tabulated for baseline, change and percent change from baseline to each scheduled visit of DB phase, Week 48 (end of DB phase), and each scheduled visit of DB extension (DBext) phase. An analysis of covariance **(**ANCOVA) model and Wilcoxon Rank Sum Test will be applied to the change and percent change from baseline to Week 48 and each scheduled visit of DB phase of efficacy parameters. All CIs for point estimates provided will be conducted using the two-sided 95% confidence intervals.

All efficacy data will be provided in listings by subject and visit.

9.1. MELD Score

MELD score is derived from the patient's serum total bilirubin, serum creatinine, and INR, as appropriate, to predict survival (Kamath 2007). MELD score will be calculated and reported for visits where these parameters are measured as described in the protocol. An increasing MELD score is associated with increased severity of hepatic dysfunction and increased 3-month mortality risk.

- Summary statistics of MELD score including baseline values, change from baseline, and Percentage change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.
- Analysis of change from baseline in MELD score will be analyzed using the Wilcoxon Rank Sum Test. The tabulation will include median, interquartile range for each treatment group, median differences and 95% CI of the median differences between treatment groups using the Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.
- MELD score will be presented in shift tables showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of patients within each shift classification (<10, 10 to <12, 12 to <13, 13 to <14, 14 to <15, and ≥15).

The MELD Score analyses will be repeated for MELD-Na

9.2. Child-Pugh (CP) Score

CP Score (Pugh 1973, Lucey 1997) is calculated and reported within the EDC system based on data entered into the eCRF by adding the scores from the 5 factors outlined in Table 2 and can range from 5-15. A total score of 5-6 is considered Grade A (mild, well-compensated disease); 7-9 is Grade B (moderate, significant functional compromise); and 10 and above is Grade C (severe, decompensated disease). Calculation of the CP score includes Investigator assessments of ascites and hepatic encephalopathy, which may be assessed during the adverse event review at

the scheduled visits, as well as total bilirubin, serum albumin, and prothrombin time, which will populate from the central laboratory.

Table 2: Child-Pugh Scoring System

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	28-35	<28
	g/dL	>3.5	2.8-3.5	<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[a]		0	Grade 1 or 2	Grade 3 or 4

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity
(Pugh 1973, Lucey 1997), Vilstrup 2014

- Baseline CP score is calculated based on components measured at Screening visit.
- Summary statistics of CP score including baseline values, change from baseline, and percentage change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.
- Analysis of change from baseline in CP score will be analyzed using the Wilcoxon Rank Sum Test. The median differences and 95% CI of the median differences between treatment groups will be constructed using the Hodges-Lehmann estimate. If the median differences between treatments are not symmetrical around the median, the Sign Test may be used.
- CP class (A, B, and C) will be presented in a shift table showing the shift from baseline to each scheduled post-baseline visit by the count and percentage of patients within each shift classification (A, B, and C).
- Components of CP score categories as listed in Table 2 will be summarized by the count and percentage of patients within each category at baseline and each scheduled post-baseline visit.

9.3. Liver Biochemistry and Hepatobiliary Damage

Liver biochemistry includes total and direct bilirubin, ALP, ALT, AST, and GGT, INR, creatinine, albumin, and platelets.

- Summary statistics of liver biochemistry including baseline values, change from baseline, and percentage change from baseline values will be provided by treatment group and by each scheduled post-baseline visit.
- Change from baseline will be analyzed by using an ANCOVA model with change from baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate.
- Percent change from baseline will be analyzed by using an ANCOVA model with percent change from baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate.
- As a sensitivity analysis, change from baseline and percent change from baseline of liver biochemistry parameters will be analyzed by using a restricted maximum likelihood (REML) based MMRM. Treatment group, time, treatment group by time interaction, and randomization stratification factor will be included as fixed effects and parameter baseline values will be included as a covariate in the model, where time includes all post baseline visits of DB phase.
- An unstructured covariance structure will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, Toeplitz, Autoregressive (1) (AR (1)) covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR (1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance-covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS. The p-value will be interpreted at 0.05 level of significance.
- The tabulation of ANCOVA model and MMRM model will include estimates of least-square (LS) means, SEs, and 2-sided 95% CIs for each treatment group. Estimates of the mean difference, SE of the difference, 2-sided 95% CI of the difference between treatment groups, and p-value will also be presented.

9.4. Total Bile Acids, Total Endogenous Bile Acids, C4 and FGF-19 Concentrations

Total bile acids, total endogenous bile acids, C4 and FGF-19 concentrations will be analyzed as follows:

- Summary statistics of total bile acids, total endogenous bile acids, C4 and FGF-19 concentrations including baseline values, change from baseline, and percentage change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.

- Change from baseline in total bile acids, total endogenous bile acids, C4 and FGF-19 concentrations at each scheduled post-baseline visit will be analyzed using the Wilcoxon Rank Sum Test.

9.5. Noninvasive Measurements of Liver Stiffness and Fibrosis

Noninvasive measurements of liver stiffness (TE) and liver fibrosis (ELF [HA, P3NP, and TIMP-1]) will be analyzed as follows:

- Summary statistics of TE and ELF including baseline values, change from baseline, and percentage change from baseline values will be provided by treatment group and by each scheduled post-baseline visit.
- Analyses of change from baseline in liver stiffness and liver fibrosis values will be analyzed by using an ANCOVA model with change from baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate.
- Analyses of percent change from baseline in liver stiffness and liver fibrosis values will be analyzed by using an ANCOVA model with percent change from baseline as the dependent variable, treatment group and randomization stratification factor as fixed effects and the baseline value as a covariate.

As a sensitivity analysis, change from baseline and percent change from baseline of these parameters will be analyzed using the same MMRM model as described in Section 9.3.

9.6. Clinical Outcome Events

The following clinical outcome events will be captured in the study:

- Time from first dose to death (all cause)
- Time from first dose to liver-related death
- Time from first dose to liver transplant
- Time from first dose to MELD score ≥15 (for patients with MELD ≤12 at baseline)
- Time from first dose to earliest hospitalization for new onset or recurrence of:
  - variceal bleed
  - hepatic encephalopathy (as defined by a West Haven score of ≥2)
  - spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis)
- Time from first dose to uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
- Time to first occurrence of any above listed clinical events

The incidence and time to first occurrence of any above listed clinical events will be summarized by treatment group using the log rank test stratified by the randomization stratification factor. The minimum and maximum time to clinical event will be presented. KM estimates of the

distribution of the time-to-event will be tabulated and graphed by treatment group. The tabulation will include the KM methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations. The number and percent of patients censored and with events will be presented. The hazard ratio and 2-sided 95% CI will be estimated based on a Cox regression model stratified by randomization strata. The proportionality of hazards will be assessed using Schoenfeld residuals.

In addition, the incidence and time to each of the above clinical events, and the incidence and time to occurrence of HCC will be summarized by treatment group using the same methods as defined above.

For the time to event analyses, subjects who do not experience an event will be censored at the time of their last contact. Subjects with no data after randomization will be considered to have an event on Day 1 (first day of IP dosing). All time-to-event endpoints include only adjudicated events.

10. SAFETY ANALYSES

Safety analyses include exposure to study treatment, treatment-emergent adverse events, clinical labs, electrocardiograms (ECGs), vital signs, and any abnormal findings observed during physical examinations after study enrollment and through discontinuation of study treatment +30 days. Safety analyses will be performed using the Safety population including by treatment groups, as defined in Section 4.3 and pooled across all active dose levels. No inferential comparison of safety endpoints will be performed, unless otherwise specified.

10.1. Exposure to Study Treatment

The duration of exposure (days) will be summarized using descriptive statistics by treatment group for DB phase, DBext phase and combined.

- Duration of exposure to IP (days) = (last treatment date – first treatment date + 1) – total duration of temporary IP discontinuation

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

- Duration of temporary discontinuation of IP = Date of restart of IP - Date of temporary discontinuation of IP + 1.

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

Total subject exposure to IP (mg) will be calculated by adding the doses taken by a subject during the DB phase, DBext phase, and combined and will be summarized using descriptive statistics. Duration of exposure to IP (days) will be categorized to following intervals: 1-21, 22-42, 43-84, 85-126, 127-168, 169-210, 211-252, 253-294, 295-336, 337-420, 421-504, 505-588, 589-672, 673-756, and >756 days. Number and percent of subjects in each interval will be tabulated by treatment group.

At each IP administration, the subject will be asked to record the reason for dose adjustment (if any). If the subject has multiple dose adjustments caused by the same reason, the subject is only counted once per reason category. Reasons for dose adjustment will be summarized by treatment group for the DB phase, DBext phase, and combined.

10.2. Treatment Compliance

Subject's overall compliance (%) with IP 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 expected to be consumed during study = total number of weeks on 5 mg once weekly + 2*total number of weeks on 5 mg or 10 mg twice weekly; during the period from first treatment date to last, inclusive

and

- number of tablets consumed during study = sum of drug taken weekly by a subject during the DB phase, DBext phase, and combined

Treatment compliance with IP will be summarized by treatment group using descriptive statistics for DB phase, DBext phase, and combined. Number and percent of patients with compliance of <60%, 60% to <80%, 80% to 120%, and >120% will be tabulated by treatment group for DB phase, DBext phase, and combined.

Subject treatment compliance will be listed based on drug administration data.

10.3. Adverse Events

Per ICH E6 (R2), an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs will be mapped to preferred terms (PTs) and system organ classes (SOCs) using MedDRA dictionary version 24.0. 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.

AEs related to COVID-19 will be flagged.

10.3.1. Treatment-emergent Adverse Events

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

- An AE starting on or after the first study drug dose and within 30 days after the last dose of study drug.

- An AE occurring prior to the first study drug dose that worsens (increase in grade) after the first study drug dose.

10.3.2. Serious Adverse Events

A serious adverse event (SAE) is any of the following untoward medical occurrences at any dose:

- 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 patient or may require medical intervention to prevent one of the outcomes listed above.

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.

10.3.3. Adverse Events of Special Interest

The following decompensation events are adverse events of special interest:

- Variceal bleeding or recurrent variceal bleeding documented by endoscopy OR patient presenting with anemia or melena (hemoglobin drop ≥2 g/dL) and found to have varices documented by endoscopy, irrespective of hospitalization or requirement of blood transfusion.
- Gastrointestinal bleeding as a result of gastric or duodenal varices verified by endoscopy
- Hepatic encephalopathy, Grade ≥2
- New onset ascites requiring treatment
- Worsening of ascites (requiring increase in drug therapy or requirement of surgical procedure such as paracentesis or shunt placement)
- Refractory ascites -unresponsive to medications, and patient is not a candidate for TIPS or shunt and requires large volume paracentesis
- Hyponatremia (Na ≤125 mEq/L) secondary to ascites
- Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis- by cell count/chemistry)

- Hepatorenal syndrome Type 1 and Type 2 and Acute Kidney Injury (AKI)
- Liver failure defined as worsening of liver synthetic function that is persistently worse relative to baseline and/or progressive over time:
  - Hepato-pulmonary syndrome
  - Porto-pulmonary syndrome
  - Liver Transplant
  - Increase in MELD scores by 3 points relative to baseline, persistent over time and unrelated to vitamin K deficiency related increase in INR
  - Any liver related event that requires hospitalization and treatment

10.3.4. TEAE Analyses

The counts and percentages of subjects experiencing a TEAE and TEAEs by PTs and SOCs in the following categories will be presented by study treatment arm:

All AE summaries will be restricted to TEAEs. Each AE summary will be displayed by treatment group for DB phase, DBext phase, and combined. Summaries that are displayed by SOC and PT will be ordered by descending order of incidence of SOC and PT within each system organ class.

Summary tables of the following TEAEs will be presented:

- Overall summary of TEAEs
- Patient incidence of TEAEs and the total number of entries by SOC and PT. This summary will be repeated for subgroups specified in Section 10.10.
- Patient incidence of TEAEs by SOC, PT, and highest severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported 1 or more events. AEs with missing severity will be considered severe for this summary.
- Patient incidence of TEAEs by SOC, PT, and closest relationship to IP (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 patient summarization, a patient is classified according to the closest relationship if the patient reported 1 or more events. AEs with a missing relationship will be considered related for this summary.
- Patient incidence of serious TEAEs and the total number of entries by SOC and PT.
- Patient incidence of TEAEs leading to IP withdrawal or study discontinuation by SOC and PT. This is a subset of the AEs where Action Taken with Study Treatment is checked as “Drug Withdrawn” or where “Patient Discontinued from Study” is checked on the eCRF.
- Patient incidence of COVID-19 related TEAEs.

Patient incidence will be summarized as subject counts and percentages unless otherwise specified.

The number of AEs and events per 100 patient years will be summarized by SOC and PT.

- Individual patient years = (the last recorded study visit date – first dose date +1)/365.25

  where: the last recorded study visit date = end of study date recorded on end of study CRF page for that patient

- Total patient years on study = sum of all individual patient years within the Safety Population
- Events per 100 patient years $= \frac{\text{Number of Event} * 100}{\text{Total Patient Years on Study}}$

The following listings will be presented by treatment group and patient:

- All AEs
- Serious AEs
- Severe AEs
- Treatment-related AEs
- AEs leading to Study Drug Withdrawal or Study Discontinuation
- AEs leading to Death
- TEAEs related to COVID-19
- Major adverse cardiovascular events (excluding deaths)

The original date and time will be shown on all listings of AEs.

10.3.5. Pruritus Adverse Events

Pruritus: Treatment-emergent pruritus, defined as any PT including "Prur" will be summarized separately by the treatment group, SOC, and PT as a subset of all TEAEs. This summary will be repeated for subjects with "new or worsened" pruritus events, as defined as follows:

- Mild, moderate, or severe treatment-emergent pruritus events in patients with no pruritus at baseline, or
- Worsening of the severity of the baseline condition in patients with pruritus at baseline.

Baseline pruritus is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose baseline severity is severe will be counted as worsening if an AE of pruritus with severe is recorded.

An analysis of treatment-emergent pruritus event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized.

In order to explore the relationship between pruritus and the IP, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent pruritus

  The time to the start of the first episode = date of onset of first episode – date of first dose of IP + 1.

Patients who never reported an AE of pruritus will be censored at the date of last contact.

- Time to onset of the first moderate or severe treatment-emergent pruritus

  The time to the start of the first moderate or severe pruritus = date of onset of the first moderate or severe pruritus – date of first dose of IP +1.

  Patients who never reported a moderate or severe AE of pruritus will be censored at the date of completion or discontinuation.

- Time to onset of the first severe treatment-emergent pruritus

  The time to the start of the first severe pruritus = date of onset of the first severe pruritus – date of first dose of IP +1.

  Patients who never reported a severe AE of pruritus will be censored at the date of completion or discontinuation.

The analysis of time to first onset of treatment-emergent pruritus AE, time to onset of the first moderate or severe treatment-emergent pruritus, and onset of the first severe treatment-emergent pruritus will include the number of patients with pruritus (first onset, first moderate or severe, first severe), the number of patients without pruritus (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The tabulation will include the KM estimate methodology using 25th, 50th (median), and 75th percentiles of the medians and corresponding 2-sided 95% CIs, if the medians can be estimated as well as percentage of censored observations. KM estimates will be plotted as a "survival curve" for each treatment group.

10.3.6. Fatigue Adverse Events

Fatigue: Treatment-emergent fatigue is defined as any PT which includes "Fatigue." New or worsened treatment-emergent fatigue is defined as follows:

- Any mild, moderate, or severe treatment-emergent fatigue events in patients with no fatigue at baseline, or
- Worsening of the severity of the baseline condition in patients with fatigue at baseline.

Baseline fatigue is defined as the Investigator's rating of severity as collected on the PBC Disease History eCRF. Patients whose baseline severity is severe will be counted as worsening if an AE of fatigue with severe is recorded.

An analysis of treatment-emergent fatigue event days per patient years on study will be performed. The days at each severity grade, including the total days of event, the total patient

years on study, and the event days per patient year on study at each severity grade, including the total, will be summarized.

In order to explore the relationship between fatigue and the IP, the following time-to-event analyses will be performed:

- Time to first onset of treatment-emergent fatigue

  The time to the start of the first episode = date of onset of first episode – date of first dose of IP + 1.

  Patients who never reported an AE of fatigue will be censored at the date of last contact.

- Time to onset of the first moderate or severe treatment-emergent fatigue

  The time to the start of the first moderate or severe fatigue = date of onset of the first moderate or severe fatigue – date of first dose of IP +1.

  Patients who never reported a moderate or severe AE of fatigue will be censored at the date of last contact.

- Time to onset of the first severe treatment-emergent fatigue

  The time to the start of the first severe fatigue will be calculated by date of onset of the first severe fatigue – date of first dose of IP +1.

  Patients who never reported a severe AE of fatigue will be censored at the data of last contact.

The analysis of time to first onset of treatment-emergent fatigue AE, time to onset of the first moderate or severe treatment-emergent fatigue, and onset of the first severe treatment-emergent fatigue will include the number of patients with fatigue (first onset, first moderate or severe, first severe), the number of patients without fatigue (censored), and the minimum and maximum times in days. KM estimates will be calculated by treatment group. The quartiles, including the median time-to-event and their corresponding 2-sided 95% CIs, will be presented. KM estimates will be plotted as a "survival curve" for each treatment group.

10.4. Clinical Laboratory Evaluations

Laboratory parameters will be summarized in standard international (SI) system of units by treatment group. Re-test or unscheduled results will not be summarized but will be included in the data listings. Baseline is defined as the mean of all available evaluations prior to treatment. All clinical laboratory data will be listed by subject and visit.

10.4.1. Hematology

Descriptive statistics will be used to summarize the results and change from Baseline to each on-study evaluation visit for hemoglobin, hematocrit, white blood count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, red blood cell count (including MCV, MCH, MCHC).

In addition, shift tables (ie, 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 by treatment group to assess changes in laboratory values from baseline to each on-study evaluation.

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 purpose, 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.

10.4.2. Chemistry

Descriptive statistics will be used to summarize the results and change from Baseline to each on-study evaluation visit for albumin, blood urea nitrogen, creatinine, aspartate aminotransferase [AST, SGOT], alanine aminotransferase [ALT, SGPT], ALP, GGT, electrolytes [calcium, chloride, potassium, sodium], glucose, total protein, and blood lipids (total cholesterol, LDL, HDL and VLDL fractions and TG), CPK, magnesium, phosphorus, bicarbonate, unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, total bilirubin, free fatty acids, TFT (TSH, free T3 and free T4).

10.4.3. Coagulation

Descriptive statistics will be used to summarize the results and change from Baseline to each on-study evaluation visit for PT, PTT, INR.

10.5. Vital Signs

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

Vital signs and weight data will be listed by subject and visit.

10.6. Electrocardiogram (ECG)

The central read ECG data will be analyzed based on methodology recommended in the International Conference on Harmonisation (ICH) E14 guideline, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonantiarrhythmic Drugs.

Overall interpretation results for 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.

ECG data will be listed by subject and visit.

10.7. COVID-19 Diagnosis

Results of COVID-19 test and if positive, whether subjects are symptomatic, will be listed by subject.

10.8. Concomitant Medications

Concomitant medications are medications that were started after the initial dose of investigational product. Concomitant medications will be mapped to Anatomic Therapeutic Chemical (ATC) class and preferred term using WHO Drug Dictionary Global B3 version, March 2021 and summarized by ATC class, preferred term, and treatment in the Safety population. Summaries will be ordered by descending order of incidence of ATC class and preferred term within each ATC class. Summary will be tabulated for the DB phase, DBext phase, and combined.

Subject with prior and concomitant medications will be presented in a data listing. Prohibited concomitant medications will be flagged in concomitant medication and presented in a data listing.

10.9. Concomitant Medical or Surgical Treatment Procedures

Concomitant medical or surgical treatment procedures are defined as all medical or surgical treatment procedures occur on or after the first dose of IP. The number and percentage of subjects who have at least one concomitant medical or surgical treatment procedures will be displayed together with the number and percentage of subjects using at least 1 concomitant medical or surgical treatment procedures within each treatment group by ATC class and preferred terms using the Safety Population.

Concomitant medical or surgical procedures will be summarized by treatment group for DB phase, DBext phase and combined. Subject concomitant or surgical procedures will be presented in data listings.

10.10. Subgroup Analyses of Safety

Adverse events will be summarized for the following subgroups of interest:

- Age Categories: <65, ≥65 years
- Sex: Male, Female

In addition, selected safety endpoints may be performed for the following defined subgroups if deemed appropriate.

- CP Class at Baseline: Class B, Class C
- Age Category: ≥75 years
- Race: White, Non-White (Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported/Unknown
- Baseline BMI: <30 kg/m2, ≥30 kg/m2

- Baseline Use of UDCA: Yes, No
- Baseline MELD score: <=12
- Baseline Rotterdam Status: Low, Moderate, High

11. PHARMACOKINETIC ANALYSES

PK analyses will be performed using the PK Population (definition in Section 4.4). PK parameters will be derived using Phoenix WinNonlin version 8.0 or higher. The PK concentrations and parameters will be available for:

- Unconjugated OCA
- Glyco-OCA
- Tauro-OCA
- Total OCA (molar sum of OCA, glyco-OCA, tauro-OCA)
- Metabolite OCA glucuronide

11.1. PK Sampling Schedule

Serial and fasting PK assessments will be performed in all patients participating in the study.

- Pharmacokinetic fasting samples prior to the study medication will be obtained from all patients on Day 1, and at Weeks 6, 12, 18, 24, 30, 36, and 48 prior to dose administration.
- Serial PK assessments will be performed in all patients at Weeks 12, 18, 24, 30, and 48 at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, and 24 hours post-dose.

The Week 6 Visit should occur 3, 4, or 5 days after the Week 6 dose (eg, if the Week 6 dose of IP is taken on a Sunday, the patient should come in for the Week 6 Visit between Wednesday and Friday). This allows for the collection of PK data near the mid-point of the weekly dosing interval (ie, 5 mg once weekly).

Patients will receive a dose of IP with approximately 240 mL of water. Patients should not drink additional water for 1 hour after taking the dose of IP and will remain fasted until after the 1-hour sample is collected. A meal replacement drink will be provided following collection of the 1-, 4-, and 7-hour PK sample. The nutritional information of the meal replacement drink should be submitted to and approved by the Sponsor in advance. No other food or drink (water is permitted) will be allowed until after the 9-hour sample collection.

The acceptable windows for the PK blood collection time points are listed in Table 3. However, because the planned non-compartmental PK analyses will use actual collection times (ie, not nominal times), data from samples collected outside of these time windows will still be included in the non-compartmental analyses. PK samples that have a collection time outside the acceptable time window will be considered as “missing” for the calculation of drug concentration summary statistics at that nominal time point.

Table 3: Acceptable Windows for Pharmacokinetic Sample Collection

Nominal Sampling Time	Acceptable Sampling Window
Before administration of IP (pre-dose or fasting)	Within 30 minutes before dosing
0.5 to 1.5 hours after IP	± 10 minutes
2 to 2.5 hours after IP	± 20 minutes
3 to 24 hours after IP	± 30 minutes

11.2. PK Endpoints

Table 4 presents the PK parameters which will be derived for all analytes where possible.

Table 4: PK Parameters

Calculation Period(s)	PK Parameter	Units	Definition
Weeks 12, 18, 24, 30, 48 with serial PK sampling	$AUC_{0\text{-}24h}$	h*ng/mL	Area under the concentration versus time curve from zero time to 24 hours. • The linear/linear trapezoidal rule should be used for estimation of AUC. • At least 4 quantifiable concentration-time values must be available to compute $AUC_{0\text{-}24h}$ • For last actual sampling times >24 hours, $AUC_{0\text{-}24h}$ will be interpolated. For last actual sampling times from 23 to 24 hours, AUC_{last} will be reported for $AUC_{0\text{-}24h}$. For last actual sampling times <23 hours, $AUC_{0\text{-}24h}$ will not be reported.
	C_{max}	ng/mL	Maximum observed concentration. If all observations are BLQ, C_{max} will be reported as zero
	C_{trough}	ng/mL	Pre-dose concentration
	T_{max}	h	First time at which C_{max} is observed. If all observations are BLQ, T_{max} will be reported as not determined (ND)
	MR_{AUC}	unitless (ratio)	The metabolite to parent ratio of $AUC_{0\text{-}24h}$ (calculated on molar basis)
	MR_{Cmax}	unitless (ratio)	The metabolite to parent ratio of C_{max} (calculated on molar basis)

11.3. Handling of Missing Data, BLQ Data, or Data Exclusions

Missing concentration data for all patients who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For all analyses (drug concentrations and PK parameters), the following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) will be imputed to zero
- The sampling time of pre-dose samples relative to dosing will also be treated as zero

Examples of potential reasons for exclusion of data from PK summary analyses include, but are not limited to:

- Subject not fasted for 8 hours prior to PK visit;
- Subject not adhering to standardized meal timing (or missed meal) during 24-hour PK profile collection;
- Non-standard dosing (eg, drug holiday, altered dose level, altered dose frequency) used prior to PK visit.

Data excluded based on this review will be included in listing outputs but will be excluded from summary tables.

11.4. Analysis of Drug Concentration Data

11.4.1. Listing of Individual Subject Drug Concentration Data

Individual subject plasma concentration data for unconjugated OCA, glyco-OCA, tauro-OCA, total OCA, and metabolite OCA glucuronide will be listed by baseline CP category, dosing regimen, subject, study visit and time point. The actual and nominal sampling times of PK blood sample collection will be listed for each subject and will include the deviation in time from the protocol scheduled time (ie, nominal time), if applicable. Columns in the listing for unconjugated OCA, glyco-OCA, tauro-OCA, total OCA, and OCA glucuronide will be displayed on the same page for each subject. Any individual concentrations excluded from summaries or analyses will be flagged and footnoted.

All measured concentrations will be presented in original units as reported by the Bioanalytical lab, ie, ng/mL.

Total OCA will be calculated as the molar sum of unconjugated OCA, glyco-OCA, and tauro-OCA in the following manner:

1. Convert units for each component of total OCA from ng/mL to μM using the molecular weight and formula:
   a. Unconjugated OCA (μM) = unconjugated OCA (ng/mL) / 420.6 g/mole
   b. Glyco-OCA (μM) = glyco-OCA (ng/mL) / 477.7 g/mole
   c. Tauro-OCA (μM) = tauro-OCA (ng/mL) / 527.8 g/mole
2. Sum molar-based components of total OCA:
   a. Total OCA (μM) = Unconjugated OCA (μM) + Glyco-OCA (μM) + Tauro-OCA (μM)
3. Convert total OCA from μM to unconjugated OCA ng/mL-equivalents:
   a. Total OCA (ng/mL) = total OCA (μM) * 420.6 g/mole

For the purpose of calculating total OCA, BLQ values for unconjugated OCA, glyco-OCA, and tauro-OCA will be imputed to zero prior to calculation of total OCA. If there is not a valid numeric value (BLQ imputations to zero are valid) for one or more of the components of total OCA (unconjugated OCA, glyco-OCA, or tauro-OCA) then total OCA will not be calculated and will be set to missing. Total OCA will be calculated in units of "unconjugated OCA ng/mL equivalents and will be reported in units of "ng/mL" in analysis outputs.

11.4.2. Summary of Drug Concentrations

Drug concentration data in ng/mL units will be summarized by analyte (OCA, glyco-OCA, tauro-OCA, total OCA, and OCA glucuronide), baseline CP category, dosing regimen, study visit and time point using the following descriptive statistics: n, number and % BLQ, arithmetic mean, SD, coefficient of variation (CV) %, minimum, median, maximum, Q1 and Q3.

The Week 6 Visit should occur 3, 4, or 5 days after the Week 6 dose. Therefore, Week 6 fasting trough PK concentrations will be summarized by 'Week 6 + 3 days', 'Week 6 + 4 days', 'Week 6 + 5 days', and 'Week 6 Combined'.

Mean concentrations for OCA, glyco-OCA, tauro-OCA, total OCA, and metabolite OCA glucuronide will not be calculated if 50% or more of the actual values at any one time point in the terminal phase are BLQ or missing.

11.5. PK Parameters Derivation

The PK parameters for OCA, glyco-OCA, tauro-OCA, total OCA, and metabolite OCA glucuronide will be estimated using concentrations in ng/ml units and actual sample collection times as follows:

- The apparent C_{max} and the corresponding T_{max} will be read directly from the concentration-time plot (observed data).
- $AUC_{0\text{-}24h}$ will be calculated in WinNonlin using a partial area with curve stripping disabled (ie, lambda z/terminal slope will not be estimated) and the linear/linear trapezoidal rule for extravascular model. The following rules apply:
  - At least 4 quantifiable concentration-time values must be available to compute $AUC_{0\text{-}24h}$
  - For last actual sampling times >24 hours, $AUC_{0\text{-}24h}$ will be interpolated. For last actual sampling times from 23 to 24 hours, AUC_{last} value will be reported as $AUC_{0\text{-}24h}$. For last actual sampling times <23 hours, $AUC_{0\text{-}24h}$ will not be reported.
    - AUC_{last} will be calculated using the linear/linear trapezoidal rule
- MR_{AUC} and MR_{Cmax} will be calculated (on a molar basis) as the metabolite to parent molar ratios of $AUC_{0\text{-}24h}$ and C_{max}.

11.5.1. Listing of Individual Subject PK Parameters

Individual subject PK parameters will be listed for the PK population by subject and include information for baseline CP category, dosing regimen, study visit, and time point.

11.5.2. PK Parameters Summarization

PK parameters will be summarized by analyte (unconjugated OCA, glyco-OCA, tauro-OCA, total OCA, and OCA glucuronide), PK parameter, baseline CP category (CP-B, CP-C, and Combined), dosing regimen, and study visit (Week 12, Week 18, Week 24, Week 30, Week 48, and All Visits). For the 'All Visits' summary, which summarizes across all visits for each dosing regimen, if a subject has data from multiple visits on a particular dosing regimen, the mean of the values across those visits will be used so that each subject is only represented once. The summary statistics to be used for each PK parameter are described in Table 5 .

Table 5: PK Summary Statistics

Variable	Summarized with:
$AUC_{0\text{-}24h}$, C_{trough}, C_{max}, MR_{AUC} and MR_{Cmax}	n, arithmetic mean, SD, CV%, minimum, median, Q1, Q3, maximum, geometric mean and geometric CV%
T_{max}	n, minimum, Q1 (25% percentile), median, Q3 (75% percentile) and maximum

The conventions in Table 6 will be used for the presentation of the descriptive statistics of PK parameters and of plasma concentrations:

Table 6: PK Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	3 significant figures or as needed based on actual measured values (for example PK concentrations) except for T_{max} which will be reported in the same precision as nominal
Mean (arithmetic and geometric), Median, Q1, Q3	3 significant figures
Standard deviation	same precision as mean and median
CV and Geometric CV	same precision as mean or geometric mean

12. PHARMACODYNAMIC ANALYSES

The ITT Population will be used for all PD analyses. Baseline is defined as the mean of all available evaluations before treatment.

12.1. PD Sampling Schedule

PD blood samples will be collected at pre-dose for Days 1, Week 6, 12, 18, 24, 30, 36 and 48 Visits. Plasma concentrations of PD biomarkers for FXR activation including C4, FGF-19, and bile acids (15 individual bile acids, 5 bile acid totals, total bile acids, and total endogenous bile acids).

12.2. PD Endpoints

- concentrations for each PD biomarker at baseline and at each study visit
- change from baseline for each PD biomarker at each study visit
- percent change from baseline for each PD biomarker at each study visit

12.3. Presentation of PD Results

12.3.1. Handling of Missing Data and BLQ Values

Missing PD biomarker data for all subjects who are administered scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values. Only samples from subjects that were confirmed fasting prior to the study visit will be included in the analyses.

PD values for C4, FGF-19, and bile acids below the assay's lower limit of quantification (LLOQ) at any point will be set to one-half the lower limit of quantification (LLOQ/2). It should be noted that a high proportion of BLQ values may affect the SD; if more than 30% of values are missing, then the SD will not be displayed. Tables of summary statistics for concentration-time data will report N (number of subjects in the analysis population), n (number of actual observations), as well as number and percentage of BLQ values.

12.3.2. Units Conversion for Bile Acids and their Sub-components

Bile acid data will be received from the laboratory in units of ng/mL and will be converted to units of µM for analysis and presentation.

Unit conversion is bile acid concentration (µM) = bile acid concentration (ng/mL) / bile acid molecular weight.

Table 7 below provides molecular weights for the 15 bile acid subcomponents. The bile acid totals will be the sum of each of the three subcomponents presented in Table 7.

For example, total UDCA (µM) = glyco-UDCA (µM) + tauro-UDCA (µM) + unconjugated UDCA (µM)

Total bile acids will be the sum of all 15 bile acids.

For example, total bile acids (µM) = total UDCA (µM) + total CDCA (µM) + total DCA (µM) + total CA (µM) + total LCA (µM).

Total endogenous bile acids will be the sum of all bile acids minus the UDCA-related bile acids.

For example, total endogenous bile acids (µM) = total CDCA (µM) + total DCA (µM) + total CA (µM) + total LCA (µM).

Table 7: Bile Acids and Their Sub-Components

Derived	Sub-Components (molecular weight)		
Total UDCA	Glyco-UDCA (449.6 g/mol)	Tauro-UDCA (499.7 g/mol)	Unconjugated UDCA (392.6 g/mol)
Total CDCA	Glyco-CDCA (449.6 g/mol)	Tauro-CDCA (499.7 g/mol)	Unconjugated CDCA (392.6 g/mol)
Total DCA	Glyco-DCA (449.6 g/mol)	Tauro-DCA (499.7 g/mol)	Unconjugated DCA (392.6 g/mol)
Total CA	Glyco-CA (465.6 g/mol)	Tauro-CA (515.7 g/mol)	Unconjugated CA (408.6 g/mol)
Total LCA	Glyco-LCA (433.6 g/mol)	Tauro-LCA (483.7 g/mol)	Unconjugated LCA (376.6 g/mol)

12.3.3. Listings and Summary Tables for PD Data

Plasma concentrations for individual bile acid subcomponent and total concentrations (unconjugated, glyco-conjugate, tauro-conjugate, and total) for UDCA, CDCA, DCA, CA, and LCA will be listed for each subject, and summarized using descriptive statistics at baseline and at each study visit stratified by baseline CP category (CP-B, CP-C, and Combined) and treatment (Placebo, 5 mg QW, 5 mg BIW, and 10 mg BIW, Combined OCA).

Total bile acids (sum of all unconjugated and conjugated bile acids for UDCA, CDCA, DCA, CA, and LCA), total endogenous bile acid (sum of all unconjugated and conjugated bile acids for CDCA, DCA, CA, and LCA), as well as concentrations of C4 and FGF-19 will also be listed for each subject and summarized using descriptive statistics at baseline and at each study visit stratified by baseline CP category (CP-B, CP-C, and Combined) and treatment (Placebo, 5 mg QW, 5 mg BIW, and 10 mg BIW, Combined OCA).

All listings and summary tables will include change from baseline and percent change from baseline data for each study visit. Additional PD analyses may be performed, if warranted by the data.

13. EXPLORATORY CORRELATION ANALYSIS BETWEEN PK AND PD

Due to the limited data available, exploratory correlation analyses between PK and PD (ie, exposure-response) will not be performed.

14. ANALYSES OF PATIENT-REPORTED OUTCOMES AND HEALTHCARE RESOURCE USE

14.1. EQ-5D-5L

The EQ-5D-5L consists of 2 sections: the descriptive system and the VAS. The descriptive system is organized into 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the patient's self-rated health on a 20-cm vertical, line with endpoints labelled "the best health you can imagine" and "the worst health you can imagine" (Herdman 2011, Oemar 2013).

Summary statistics of EQ-5D-5L data including baseline values and change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.

14.2. PBC-40

The PBC-40 is a validated disease-specific 40-question quality of life questionnaire, which consists of 6 domains: General Symptoms, Itch, Fatigue, Cognitive Function, Social, and Emotional (Jacoby 2005).

Summary statistics of PBC-40 data including baseline values and change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.

14.3. Pruritus Visual Analog Scale

Pruritus Visual Analog Scale (VAS) will be used to assess pruritus in individual patients.

Summary statistics of Pruritus VAS data including baseline values and change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.

14.4. Chronic Liver Disease Questionnaire

The CLDQ is a disease-specific health related quality of life questionnaire for patients with chronic liver disease. The questionnaire includes 29 items in the following domains: fatigue, activity, emotional function, abdominal symptoms, systemic symptoms, and worry). Each question is answered on a scale from 1 (always) to 7 (never) with a higher score corresponding to a better quality of life. The CLDQ produces a summary score and domain scores that correlate with the severity of liver disease (Younossi 1999).

Summary statistics of CLDQ data including baseline values and change from baseline values will be presented by treatment group and by each scheduled post-baseline visit.

15. DEVIATIONS FROM PROTOCOL

- As a sensitivity analysis, liver biochemistry parameters will be analyzed by using a restricted maximum likelihood (REML) based mixed model repeated measures (MMRM), time, the treatment group by time interaction, and the randomization stratification factor will be included as fixed effects and the baseline value will be included as a covariate in the model, where time includes all post baseline visits of DB phase.
- A sensitivity analysis will be analyzed for liver stiffness and liver fibrosis (ELF [HA, P3NP, and TIMP-1]) as described for liver biochemistry parameters.
- Analysis of Total endogenous bile acids is added.
- Summary of baseline Rotterdam status is added.
- Summary of subject disposition and protocol deviations for Non-COVID-19 Impacted Population are added.
- COVID-19 Diagnosis is added.
- COVID-19 AEs are flagged.

16. REFERENCES

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Younossi ZM, Guyatt G, Kiwi M, et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic disease. Gut. 1999;45(2):295-300.

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 (SE), median, 25th and 75th quartiles, minimum, and maximum values.

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

General Methods

- Summaries will be presented for each treatment and overall for subjects disposition, demographics and baseline characteristics, medical history, disease history, prior medications, and historical procedures summary tables. Summaries will be presented for each treatment for other tables.
- All subjects and relevant data entered into the database will be included in subject data listings, including screen failures, where applicable.
- All data listings that contain an evaluation date will contain a relative study day as defined in below.
- For categorical variables, summary tabulations of the number and percentage of patients within each category 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. The category for missing data will not have percentage.
- For continuous variables, the number of patients, mean, standard deviation (SD), standard error of the mean (SE), median, Q1, Q3, minimum, and maximum values will be presented. The precision of summary statistics, unless otherwise, specified will be as follows:
  - minimum, maximum: same decimal place as the raw data,
  - mean, median, Q1, and Q3: 1 more decimal place than the raw data,
  - SD and SE: 2 decimal places more than the raw data.
- In general, the decimal places should not exceed 3 decimal places unless appropriate. 95% confidence intervals (CIs) will be provided and will be rounded to 1 decimal place.

- For results from an analysis of covariance (ANCOVA) model or a mixed model repeated measures (MMRM), least square (LS) mean and LS mean difference will be presented with one decimal place, and standard error (SE) of LS means and SE of LS mean difference will be presented with two decimal places.
- p-value will be presented with 3 decimal places.
- Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs.

Key Definitions

First Dose Date

First dose date is defined as the day of first dose of IP received after randomization.

Last Dose Date

Last dose date is defined as day of the last dose of IP. For subjects ongoing at time of analysis, last dose date will be considered the date of the most recent study visit in the database for that subject.

Study Day

The study day is determined relative to the date of first dose of IP. The day of the first dose of IP will be defined as study day 1. The day prior to the first dose of IP is study day -1. There is no study day 0.

For events that occur before the first dose of IP, study day = date of the event – first dose date; for events that occur on or after the first dose of IP, study day = date of the event – first dose date + 1.

Time to Event

The time to an event will be calculated in days as the date of the first occurrence of the event - the date of first IP administration + 1.

The time to a pre-treatment adverse event will be calculated as the date of first IP administration - the date of the first occurrence of the adverse event.

Baseline and Change from Baseline

The baseline value for statistical analyses of quantitative parameters is defined as the mean of all available evaluations prior to the first administration of IP, unless otherwise specified. Values collected at unscheduled visits prior to the start of the IP administration will be included in the calculation of baseline values. If there is only one evaluation prior to the first administration of IP then the available data from this evaluation will be used as the baseline value.

The baseline value for analyses of lipid parameters is defined as the last fasted evaluation prior to the first administration of IP.

The baseline value for analyses of qualitative parameters (eg, normal/abnormal) is defined as the last evaluation prior to the first administration of IP.

Baseline values defined above will not change regardless if a subject stops taking IP and begins taking commercially marketed OCA.

Change from baseline = (post-baseline value – baseline value).

Percent change from baseline = 100*(post-baseline value – baseline value)/ baseline value

For the purpose of tabulations, the unscheduled post-baseline values generally will be excluded from summary tables, but will be included in data listings. Unscheduled visits will be considered for analyses of shift from baseline to worst value (low-normal-high).

Dose Regimen

Following the discussion in Section 3, dose regimen for each clinical visit after first dose up to Week 12 Visit is OCA 5 mg once weekly; dose regimen after Week 12 Visit could be OCA 5 mg once weekly for patient not up-titrated or OCA 5 mg twice weekly for patient up-titrated; and dose regimen after Week 18 Visit could be OCA 5 mg once weekly, 5 mg twice weekly, or 10 mg twice weekly based on patient titration (up-titrated or down-titrated) history prior to the visit. For example, if an up-titration to 5 mg twice weekly is given to a patient at Week 12 Visit, this regimen should be the one for this patient at Week 18 visit.

Missing Data

All available data of the subjects who withdraw from the study for any reasons will be analyzed. Missing data will be assumed to be missing at random. There will be no imputation of missing data for the analysis purpose. Change from baseline of an endpoint will be missing when either baseline value of the endpoint is missing or post-baseline value of the endpoint is missing.

Incomplete start and end dates for adverse events and concomitant medications are imputed as follows:

Incomplete Start Date:

Missing day and month

- If the year is the same as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is prior to the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is after the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the same as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If the year of the partial date is before the year of the first dosing date or the year of the partial date and the first dosing date are the same but the month of partial date is

before the month of the first dosing date, then the last day of the month will be assigned to the missing day.

- If either the year of the partial date is after the year of the first dosing date or the year of the partial date and the first dose date are the same but the month of partial date is after the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year

- No imputation is needed.

Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is after the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is not equal to the year of the last dosing date or the year of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed.

Visit Windows

Visit windows are specified in the Table 1 of the protocol - Schedule of Study Procedures for the 2 phases of the study: DB phase and DBext phase. All data will be tabulated per the evaluation visits as recorded on the electronic case report form (eCRF) even if the assessment is outside of the visit window. In data listings, the study day of all dates will be presented. Data collected at unscheduled visits that occurred outside the time windows specified will be included in the data listings but will not be included in the analyses unless otherwise stated.

Pooling of Centers

Data from all study centers will be combined for analysis.