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Albireo AB, an Ipsen Company

A3907-002

An Open Label, Phase 2 Study to Evaluate the Effect of A3907 on Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Adults with Primary Sclerosing Cholangitis (PSC)

16SEP2025
Final Statistical Analysis Plan

Version 1.0

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Version History

Version	Date	Reasons for Amendment
Version 1.0	16 September 2025	Final Version 1.0

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List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASBT	Apical Sodium Bile Acid Transporter
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Plasma Concentration Time Curve
BID	Twice Daily
BMI	Body Mass Index
C4	7α-Hydroxy-4-Cholesten-3-One
CA	Cholic Acid
CA-S	Cholic Acid-Sulfate
CA 19-9	Carbohydrate Antigen 19-9
CDCA	Chenodeoxycholic Acid
CDCA-S	Chenodeoxycholic Acid-Sulfate
C_{max}	Maximum Plasma Concentration
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRS	Clinically Relevant Stricture
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DCA	Deoxycholic Acid
DCA-S	Deoxycholic Acid-Sulfate
DILI	Drug-Induced Liver Injury
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELF	Enhanced Liver Fibrosis
EOT	End of Treatment
EOS	End of Study
ERCP	Endoscopic Retrograde Cholangiopancreatography
FGF-19	Fibroblast Growth Factor 19
GCA	Glycocholic Acid
GCA-S	Glycocholic Acid-Sulfate
GCDCA	Glycochenodeoxycholic Acid
GCDCA-S	Glycochenodeoxycholic Acid-Sulfate
GDCA	Glycodeoxycholic Acid
GDCA-S	Glycodeoxycholic Acid-Sulfate
GGT	Gamma-Glutamyl Transferase
GLCA	Glycolithocholic Acid
GLCA-S	Glycolithocholic Acid-Sulfate
GUDCA	Glycoursodeoxycholic Acid

GUDCA-S	Glycoursodeoxycholic Acid-Sulfate
HÁ	Hyaluronic Acid
hCG	Human Chorionic Gonadotropin
hsCRP	High-Sensitivity C-Reactive Protein
LBT	Liver Biochemical Test
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	International Normalized Ratio
IXRS	Interactive Voice/Web Response System
LCA	Lithocholic Acid
LCA-S	Lithocholic Acid-Sulfate
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein Cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model For End Stage Liver Disease
MIST	Metabolites in Safety Testing
MMP	Matrix Metalloproteinase
MRCP	Magnetic Resonance Cholangiopancreatography
NRS	Numerical Rating Scale
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PSC	Primary Sclerosing Cholangitis
PR	Pulse Rate
PT	Prothrombin Time
PT	Preferred Term
QD	Once Daily
QTcF	Corrected QT Interval Based on Fridericia's Formula
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SRC	Safety Review Committee
TBL	Total bilirubin
TCA	Taurocholic Acid
TCDCA	Taurochenodeoxycholic Acid
TDCA	Taurodeoxycholic Acid
TEAE	Treatment-Emergent Adverse Event
TIMP1	Tissue Inhibitor of Metalloproteinase 1
TLF	Tables, Listings, and Figures
TLCA	Taurolitocholic Acid

TUDCA	Tauroursodeoxycholic Acid
UDCA	Ursodeoxycholic Acid
UDCA-S	Ursodeoxycholic Acid-Sulfate
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1. Introduction

A3907 is an oral, systematically available, potent inhibitor of the apical sodium bile acid transporter (ASBT). Primary sclerosing cholangitis (PSC) is a rare, life-threatening, chronic cholestatic liver disease characterised by progressive destruction of the intra-and/or extrahepatic ducts resulting in cirrhosis and its complications. The study is designed to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of A3907 in patients with PSC. The dose selected is expected to reduce bile acid transport, leading to a net loss in serum bile acids, and positively influence liver enzyme and markers of liver fibrosis.

This document outlines the statistical methods to be implemented in the analysis of data collected within the scope of the Protocol for the Study A3907-002, An Open Label, Phase 2 Study to Evaluate the Effect of A3907 on Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Adults with Primary Sclerosing Cholangitis (PSC).

The purpose of this statistical analysis plan (SAP) is to define the planned statistical methods consistent with the study objectives. This plan should be read in conjunction with the study protocol version 3.0 (14 July 2023) and the case report forms (CRFs) version 5.0 (Date: 07 Aug 2024). All analyses will be conducted using Statistical Analysis System (SAS)® Version 9.4 or higher. This SAP will be based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 guidelines.

2. Objectives

2.1. Primary Objective

To evaluate the safety and tolerability of A3907 in patients with PSC with and without a Clinically Relevant Strictures (CRS) following repeat doses.

2.2. Secondary Objectives

- To evaluate the PK of A3907
- To evaluate the effect of A3907 on bile acid levels
- To evaluate the effect of A3907 on liver health
- To evaluate the effect of A3907 on bile acid synthesis

2.3. Exploratory Objectives

- To explore the effect of A3907 on markers of liver inflammation and fibrosis.
- To evaluate the effect of A3907 on symptoms.
- To explore the effect of A3907 on episodes of cholangitis (for patients with available 12-week data prior to single dosing).

Additional exploratory objectives, Arm 4 only:

- To evaluate the effects of A3907 on survival without a liver transplant.
- To evaluate the effect of A3907 on bile duct function

3. Investigational Plan

3.1. Overall Study Design and Plan

This is an open-label, Phase 2 study to evaluate the safety, tolerability, PK, and PD effects of three (3) dose levels of A3907, 10 mg (Arm 1), 30 mg (Arm 2) administered orally once daily (QD), or 30mg twice daily (BID) in Arms 3 and 4 for 12 weeks in patients with PSC with and without CRS (Figure 1). Eligible patients must have a clinical diagnosis of large-duct PSC obtained by appropriate biliary imaging, and evidenced by chronic cholestasis of more than 6 months duration. Patients must also have serum bile acids above the upper limit of normal (ULN) at Screening Visit and alkaline phosphatase (ALP) levels > 1.5 × ULN but ≤ 10 × ULN repeated at least 2 weeks apart for baseline to reflect variability of < 30%. If variability is > 30%, a third ALP level may be obtained to determine the direction of abnormality or document stability. If stable (< 30% variance) the patient may be enrolled.

Prior to any other study procedures being conducted, the patient will have the nature of the study explained to him/her and be asked to sign an informed consent form (ICF). Informed consent must be obtained prior to any study procedures that do not form a part of the patient's normal care. After signing the ICF, patients will be evaluated for study eligibility. If not fasting at time of consent, patient will return to complete screening assessments after having fasted for 4 hours.

The study will include up to a 2-week Screening Period, followed by administration of a single dose of A3907, followed by a 2-week period to confirm the target exposure is reached before beginning a treatment period of 12 weeks (Figure 1). There will be a total of 8 scheduled visits during the study (including 1 Screening Visit).

Figure 1: Study Design

*EASL defined MRCP Equivalent of clinically relevant strictures: A biliary stricture on MRI/MRCP with > 75% reduction of duct diameter in the common bile duct or hepatic ducts
BID = twice daily; f/u = follow up; PK = pharmacokinetic; QD = once daily; wks = weeks; EASL = European Association for the Study of the Liver

Enrolment into the treatment arms will be staggered with Arm 2 beginning after at least 3 patients in Arm 1 have completed 2 weeks of treatment and an internal Safety Review Committee (SRC) has reviewed safety and PK data. Enrolment into Arms 3 and 4 will occur concurrently beginning after at least 3 patients in Arm 2 have completed 2 weeks of treatment and an internal SRC has reviewed safety and PK data.

The last dose of study drug will be administered at Week 12 (Visit 7) and the End-of-Study Visit (Visit 8) will take place 14 days later. Patients who prematurely discontinue from the study for any reason will undergo End-of-Treatment procedures at the time of discontinuation and End-of-Study procedures within 14 days after the last dose of study drug. Except for patients that discontinue due to an adverse event (AE), withdrawn or terminated early patients may be replaced, as needed, to ensure 6 patients are enrolled into the 12-week Treatment Period of each treatment arm. The end of the study is defined as the time when the last patient completes their last visit.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary endpoint is safety and tolerability as determined by the incidence of treatment-emergent adverse events (TEAEs) through Week 12.

3.2.2. Secondary Endpoints

- PK parameters for A3907 including, but not limited to, maximum observed plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC).
- Change from Baseline to Week 12 in serum, urine and individual and total bile acid levels.
- Change from Baseline to Week 12 in liver biochemical tests (LBTs): aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and total and direct bilirubin levels.
- Change from Baseline to Week 12 in 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF-19)

3.2.3. Exploratory Endpoints

The exploratory endpoints are:

- Change from Baseline to Week 12 in autotaxin
- Change from Baseline to Week 12 in ProC3
- Change from Baseline to Week 12 in high-sensitivity C-reactive protein (hsCRP)
- Change from Baseline to Week 12 in matrix metalloprotease 7 (MMP7) and matrix metalloprotease 9 (MMP9)
- Change from Baseline to Week 12 in enhanced liver fibrosis (ELF) and Mayo-PSC score
- Change from Baseline to Week 12 in carbohydrate antigen 19-9 (CA 19-9)
- Change from Baseline to Week 12 in liver stiffness as assessed by FibroScan
- Changes from baseline to Week 12 in pruritus using the daily pruritus scores captured via the pruritus numerical rating scale (NRS)
- Change from Baseline to Week 12 in fatigue using the daily fatigue scores captured via the fatigue NRS
- Change from Baseline to Week 12 in sleep disturbance using the daily sleep disturbance scores captured via the sleep disturbance NRS
- Change from Baseline to Week 12 in mood using the daily mood scores captured via the mood Likert scale
- Episodes of cholangitis requiring antibiotic use in the 12 weeks prior to single dosing versus the 12 weeks after dosing

Additional exploratory endpoints, Arm 4

- Change of model for end stage liver disease (MELD) from baseline to Week 12
- Change in endoscopic biliary dilation intervals/ frequency in the 12 weeks prior to single dosing (V2) compared to the 12-week treatment period for those patients who are regularly dilated.

3.3. Treatments

In this 12-week study, A3907 doses of 10 mg and 30 mg QD (Arms 1 and 2, respectively), and 30 mg BID (Arms 3 and 4) in a tablet formulation will be administered orally to 6 patients per arm. These doses are expected to result in exposures predicted to be pharmacodynamically active. Approximately 24 patients are expected to be treated in this study with six patients in each of the four treatment arms of the study.

3.3.1. Treatments Administered

The study includes up to a 2-week Screening Period, followed by administration of a single dose of A3907, followed by a 2-week period to confirm target exposure is reached before beginning a treatment period of 12 weeks. Each patient's PK will be reviewed and, if the systemic exposures do not exceed the highest systemic exposure previously established in the SAD portion of the FIH study (C_{max} of [CCI] ng/mL or AUC of [CCI] ng h/mL), the dose will be confirmed and the patient will begin administration of A3907 daily for 12 weeks. If the exposures exceed the highest systemic exposure, the individual patient will be terminated early.

Study drug will be dispensed to the patient at defined intervals from Visit 3 through Visit 7, together with instructions on how to store and take the drug. Study drug administration data, including whether each patient took each dose, will be documented through the Patient Diary and transferred to the study database at each visit.

4. General Statistical Considerations

In general, descriptive statistics will be presented by treatment arm and by visit, as applicable. Continuous data will be summarised using descriptive statistics (i.e., n, mean, standard deviation (SD), or standard error (SE), median, minimum, and maximum). Categorical data will be summarised using the patient count and percentage in each category. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported up to a maximum of three decimal places. Mean and median will be displayed to one level of precision greater than the data collected up to a maximum of three decimal places. Standard deviation and standard error will be displayed to two levels of precision greater than the data collected up to a maximum of four decimal places. When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. Unless otherwise specified, all confidence intervals (CI) will be 2-sided and performed using a 5% significance level. Confidence intervals will be

displayed to two levels of precision greater than the data collected up to a maximum of three decimal places. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of patients in that treatment arm within the population of interest, unless otherwise specified. Refer to the Appendix 1 for imputation rules for partial and missing AE onset dates as well as partial and missing prior/concomitant medication start and end dates. Data will be displayed in all listings sorted by treatment arm.

4.1. Sample Size

Due to the exploratory nature of this study, no formal power calculations will be used to determine sample size. Approximately 24 patients will be enrolled with six (6) patients in each treatment arm. To ensure 6 patients are enrolled into the 12-week Treatment Period of each treatment arm, patients that discontinue due to an adverse event, withdrawn or terminated early patients may be replaced as needed.

4.2. Randomization, Stratification, and Blinding

Blinding is not applicable since this is an open-label study. All patients will take A3907 administered orally daily at approximately the same time each day. Patients will be assigned to treatment arms via an interactive voice/web response system (IXRS).

4.3. Analyses Set

4.3.1. Screened Set

The screened set will include all screened patients who signed the study informed consent, including screen failures.

4.3.2. Enrolled Set

The enrolled set will include all screened patients who signed the study informed consent and met the study eligibility criteria.

4.3.3. Safety Analysis Set

The safety analysis set will include all patients who received at least 1 dose of A3907 and will be used for all analyses except PK and PD analyses.

4.3.4. Pharmacokinetic Analysis Set

The PK analyses set will consist of all patients who received at least one dose of A3907 and have evaluable PK data (i.e. with no major protocol deviation affecting the PK variables). The PK analysis set will be used for all PK analyses.

4.3.5. Pharmacodynamic Analysis Set

The PD analyses set will include all patients who received at least one dose of A3907 and for whom at least one PD marker can be evaluated. The PD analysis set will be used for all PD analyses.

4.4. Study Day

Study Day 1 is defined as the date of first single dose. The reference date for the calculation of study days will be Study Day 1. For some analysis purposes, study day is calculated as:
Date of assessment – Day 1 +1, for assessments done after first dose of study drug;
Date of assessment – Day 1, for assessments done before the first dose of study drug.
The screening period for the study will be from Day -14 (±2) to Day 1. The single dose will be administered on Day 1/Visit 2. The 12-week treatment period will be from Visit 3 to Visit 7. The End-of-Study Visit will occur on Visit 8.

4.4.1. Overall Treatment Baseline Value (Baseline 1)

For demographics, TEAE, medical and surgical History, prior/concomitant medications, baseline 1 is defined as the last non-missing assessment prior to the first study drug administration.

For other assessments, unless otherwise specified (as for serum biomarkers, clinical chemistry assessments and urinalysis tests with quantitative results, faecal calprotectin assessments, episodes of cholangitis requiring antibiotic use, endoscopic biliary dilation intervals/frequency and NRS analysis below), the baseline 1 value of a parameter is defined as the last non-missing assessment of that parameter prior to the study drug administration of planned single dose.

For serum bile acid assessments, clinical chemistry assessments and urinalysis tests with quantitative results, baseline 1 is defined as the average of all Screening results and results on the day of the planned single dose if both results are available. Otherwise, baseline 1 will be defined as the last non-missing assessment prior to the study drug administration of planned single dose.

For other serum biomarkers and faecal calprotectin assessments, baseline 1 is defined as the assessment performed on the day of the planned single dose.

For episodes of cholangitis requiring antibiotic use, endoscopic biliary dilation intervals/frequency, baseline 1 is defined as data collected on the day of the planned single dose, which are assessments of 12 weeks prior to Single Dosing.

For NRS analysis, baseline 1 will be calculated by averaging the two weekly scores obtained prior to the day of the planned single dose.

4.4.2. 12-Week Treatment Period Baseline Value (Baseline 2)

For assessments that are interested in the change from baseline 2 during the 12-week treatment period, baseline 2 is defined as the last non-missing value of the assessment prior to the 12-week treatment period.

4.5. Visit Windows

Analysis visit windows will be defined for analysis purposes and for summary tables presented by visit. Both scheduled and unscheduled assessments will be considered as valid assessments for analysis.

Analysis visit labels will be assigned to each record based on the study day windows relative to the date of the planned single dose of study drug.

To support the definition of analysis window, study day compared to the date of the planned single dose is calculated as:

Date of assessment – Date of the planned single dose +1, for assessments done after planned single dose of study drug;

Date of assessment – Date of the planned single dose, for assessments done before planned single dose of study drug.

Table 1: Analysis Visit Window (General)

TIMING OF ASSESSMENT	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	ANALYSIS WINDOW (STUDY DAY)
Visit 1	Baseline		≤ -1
Visit 2	Baseline		1 (Pre-dose)
Visit 3	Start of 12-Week Treatment	14	Post-baseline – 22
Visit 4	Week 2 of 12-Week Treatment	28	23 – 36
Visit 5	Week 4 of 12-Week Treatment	42	37 – 57
Visit 6	Week 8 of 12-Week Treatment	70	58 – 85
Visit 7	Week 12 of 12-Week Treatment	98	86 – last dose day* + 7
Visit 8	Follow-Up after 12-Week Treatment	112	≥ last dose day* + 8

Note: This table shows assessments for vital signs, blood sampling for serum total and individual bile acids, urinalysis, and clinical chemistry.
EOT=end of treatment.
*The later of (Last dose day, EOT visit day) will be used.

Table 2: Analysis Visit Window for Specific Assessments

ASSESSMENT(S)	TIMING OF ASSESSMENT	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	ANALYSIS WINDOW (STUDY DAY)
BLOOD SAMPLING FOR FGF-19	Visit 2	Baseline		≤ 1 (Pre-dose)
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 29
	Visit 5	Week 4 of 12-Week Treatment	42	30 – 71
	Visit 7	Week 12 of 12-Week Treatment	98	72 – last dose day* + 7
BLOOD SAMPLING FOR C4	Visit 2	Baseline		≤1 (Pre-dose)

ASSESSMENT(S)	TIMING OF ASSESSMENT	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	ANALYSIS WINDOW (STUDY DAY)
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 29
	Visit 5	Week 4 of 12-Week Treatment	42	30 – 71
	Visit 7	Week 12 of 12-Week Treatment	98	≥ 72
BLOOD SAMPLING FOR BIOMARKERS	Visit 2	Baseline		≤ 1 (Pre-dose)
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 29
	Visit 5	Week 4 of 12-Week Treatment	42	30 – 71
	Visit 7	Week 12 of 12-Week Treatment	98	72 – last dose day* + 7
	Visit 8	Follow-Up after 12-Week Treatment	112	≥ last dose day* + 8
URINE SAMPLING FOR INDIVIDUAL AND TOTAL BILE ACIDS	Visit 2	Baseline		<= 1 (24-hour Pre-Dose period)
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 29
	Visit 5	Week 4 of 12-Week Treatment	42	30 – 71
	Visit 7	Week 12 of 12-Week Treatment	98	72 – last dose day* + 7
	Visit 8	Follow-Up after 12-Week Treatment	112	≥ last dose day* + 8
HEMATOLOGY	Visit 1	Baseline		≤ -1 (Pre-dose)
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 22

ASSESSMENT(S)	TIMING OF ASSESSMENT	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	ANALYSIS WINDOW (STUDY DAY)
	Visit 4	Week 2 of 12-Week Treatment	28	23 – 36
	Visit 5	Week 4 of 12-Week Treatment	42	37 – 57
	Visit 6	Week 8 of 12-Week Treatment	70	58 – 85
	Visit 7	Week 12 of 12-Week Treatment	98	86 – last dose day* + 7
	Visit 8	Follow-Up after 12-Week Treatment	112	≥ last dose day* + 8
Pruritus NRS lead question	Visit 1	Baseline		≤ -1
COAGULATION	Visit 1	Baseline		≤ -1
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 29
	Visit 5	Week 4 of 12-Week Treatment	42	30 – 71
	Visit 7	Week 12 of 12-Week Treatment	98	72 – (last dose day* + 7)
12 LEAD ECG	Visit 1	Baseline		≤ -1
	Visit 2	Baseline		1 (Pre-dose)
	Visit 5	Week 4 of 12-Week Treatment	42	Post-baseline – 71
	Visit 7	Week 12 of 12-Week Treatment	98	72 – (last dose day* + 7)
ENDOSCOPIC BILIARY DILATION DATA	Visit 2	Baseline		<=1 (Pre-dose)
	Visit 7	Week 12 of 12-Week Treatment	98	Post-baseline – (last dose day* + 7)

ASSESSMENT(S)	TIMING OF ASSESSMENT	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	ANALYSIS WINDOW (STUDY DAY)
PHYSICAL EXAMINATION	Visit 1	Baseline		≤ -1
	Visit 2	Baseline		1 (Pre-dose)
	Visit 5	Week 4 of 12-Week Treatment	42	Post-baseline – 71
	Visit 7	Week 12 of 12-Week Treatment	98	72 – (last dose day* + 7)
	Visit 8	Follow-Up after 12-Week Treatment	112	≥ last dose day* + 8
FAECAL CALPROTECTIN	Visit 2	Baseline		<=1 (Pre-dose)
	Visit 3	Start of 12-Week Treatment	14	Post-baseline – 22
	Visit 4	Week 2 of 12-Week Treatment	28	23 – 36
	Visit 5	Week 4 of 12-Week Treatment	42	37– 57
	Visit 6	Week 8 of 12-Week Treatment	70	58– 85
	Visit 7	Week 12 of 12-Week Treatment	98	86 – (last dose day*+7)
	Visit 8	Follow-Up after 12-Week Treatment	112	≥ last dose day*+8
FIBROSCAN	Visit 1	Baseline		≤ -1
	Visit 3	Start of 12-Week Treatment	15	Post-baseline – 29
	Visit 5	Week 4 of 12-Week Treatment	43	30 – 71
	Visit 7	Week 12 of 12-Week Treatment	99	72 – (last dose day* + 7)

ASSESSMENT(S)	TIMING OF ASSESSMENT	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	ANALYSIS WINDOW (STUDY DAY)
	Visit 8	Follow-Up after 12-Week Treatment	113	≥ last dose day* + 8

Note: This table shows assessments for specific visits.
C4=7α-hydroxy-4-cholesten-3-one; FGF-19=fibroblast growth factor 19; NRS= numerical rating scale; ECG= electrocardiogram; EOT=end of treatment .
*The later of (Last dose day, EOT visit day) will be used.

5. Patient Disposition

5.1. Disposition

Disposition will be summarised for all enrolled patients by treatment arm and overall. The number and percentage of patients who have been enrolled, have been treated (i.e., Safety analysis set), have completed the study treatment, have completed the study, have discontinued from the study treatment, have discontinued from the study, as well as the primary reason for the study treatment discontinuation and the study discontinuation will be tabulated.

Additionally, a summary of the analysis sets will be provided to include the number and percentage of patients in each analysis set by treatment arm and overall. A summary of the analysis sets by treatment arm and country will also be presented. Patient disposition, analysis sets and screen failures will be presented in a listing.

5.2. Protocol Deviations

Protocol deviations will be recorded within the PPD Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock. In addition, protocol deviation classification (i.e., significant vs. non-significant) as determined by sponsor prior to database lock will be documented in CTMS. Protocol Deviations related with COVID-19 will be assessed and reported accordingly.

The number and percentage of patients with significant protocol deviations will be summarised by CTMS activity subtype, treatment arm and overall using the Safety analysis set. Individual patient protocol deviations, both significant and non-significant, will be presented in a data listing using the Enrolled set.

6. Demographics and Baseline Characteristics

6.1. Demographics

Baseline demographics will be summarised by treatment arm and overall, for all patients in the Safety analysis set. Baseline demographic data to be evaluated will include age, sex, geographical origin, fertility status, height (cm), weight (kg) and body mass index (BMI) (kg/m^2). Descriptive statistics will be presented for age (18-75 years inclusive), height and weight. Sex, geographic origin, and fertility status will be summarised categorically. Demographic and baseline characteristics data will be listed for all patients in the Safety analysis set.

6.2. Medical and Surgical History

Medical and surgical history will be summarised by treatment arm and overall, for all patients in the safety analysis set. Medical and surgical history data will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The dictionary version used for reporting the study will be described in the relevant table and listing footnotes. Percentages will be calculated based on the number of patients in the Safety Analysis Set. Medical history will be coded using MedDRA Version 28.0.

Medical history data including specific details will be presented in a listing.

6.3. Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 7.2.2 and 7.2.3 of the protocol. All inclusion/exclusion criteria related information for enrolled patients will be presented in a data listing. The listing will include those failed inclusion/exclusion criteria.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug B-3 Dictionary dated March, 2025. The WHO Drug Dictionary version used for reporting the study will be described in the relevant table and listing footnotes. If the medication start or end date is missing, it will be imputed before summary as described in Appendix 1. If the start date of a medication is completely missing and the end date is within 14 days before the dosing of study drug on Day 1, it will be counted as a prior medication. If the start date of a medication is completely missing and the end date is after the dosing of study drug on Day 1 it will be counted as both a prior and concomitant medication. If the start date of a medication is on or after the dose of study drug on Day 1 and the end date of the medication is completely missing, it will be counted as a concomitant medication. Prior and concomitant medications will be summarised and listed based on the Safety analysis set.

7.1.1. Prior Medications

Prior medications are defined as those medications taken by a patient within 14 days prior to the first intake of study drug. The total number of prior medications will be summarised. The number and percentage of patients with at least one prior medication will be summarised overall and by Anatomical Therapeutic Chemical (ATC) level 4 term and PT. Prior medications will be presented by treatment and overall using the Safety Analysis Set. Medications will be listed in a descending order by ATC level 4 category based on the Overall of all treatment arms. Within each ATC level 4 category, PTs will be listed in an alphabetical order.

7.1.2. Concomitant Medications

Concomitant medications are defined as those non-study medications taken on or after the first day of study drug dose through 14 days after the last dose of study drug. The total number of concomitant medications will be summarised in a table. The number and percentage of patients with at least one concomitant medication will be summarised by ATC level 4 term and PT. Concomitant medications will be presented by treatment and overall using the safety analysis set. Medications will be listed in a descending order by ATC level 4 category based on the Overall of all treatment arms. Within each ATC level 4 category, PTs will be listed in an alphabetical order.

7.2. Study Drug Administration

Onsite study drug administration will be listed for each patient in the Safety analysis set.

7.3. Study Treatments

7.3.1. Extent of Exposure

Treatment Exposure will be displayed by the single dose (Day 1 to Day 14) and 12-week (Day 15 to Day 112) treatment periods. For single dosing period, number of patients who received the single dose will be presented based on the Safety Analysis Set. Duration of 12-week treatment period exposure is defined as the total number of days a patient is exposed to the study drug during the 12-week treatment period. Duration of 12-week treatment period exposure will be presented as the total number of days from the first dose date and time in the 12-week treatment period to the last dose date and time (date of last known study drug administration minus the date and time of first dose in the 12-week treatment period + 1) as recorded on the End of Treatment electronic case report form (eCRF). If the last dose date and time on the End of Treatment page is missing, then the last dose date and time recorded on the A3907 Administration page of eCRF will be used. Duration of 12-week treatment period will be categorized into time intervals and frequency counts and percentages will be presented for the number (%) of patients in each interval. The time intervals will be grouped into the following categories: 1 to 14 days, > 14 to ≤ 28 days, > 28 to ≤ 42 days, > 42 to ≤ 70 days, > 70 to ≤ 98 days, and > 98 days. Duration of exposure will also be summarised using descriptive statistics. For 12-week treatment period summary, percentages will be computed from the number of patients in the Safety Analysis Set who actively entered 12-Week treatment period. All doses will be included in the listing based on the Safety Analysis Set.

7.3.2. Treatment Compliance

Compliance will be calculated as: Treatment Compliance = 100 × ([Number of study drug dispensed – number of study drug returned] across the 12-week treatment period/number of study drug that should be taken). The total number of tablets actually taken is the total number of tablets recorded as taken based on the eCRF (number of tablets dispensed minus returned) summed over the 12-week treatment period. If the number of tablets returned is confirmed as missing and the study drug is confirmed as not been returned, the derivation will not be done. Treatment compliance overall and by treatment will be summarised using descriptive statistics and following categories: < 80%, ≥ 80%-≤ 100%, > 100%-≤ 120% and > 120%. A listing of Study Drug Compliance will be presented based on the number of patients in Safety Analysis Set who actively entered 12-Week treatment period.

8. Secondary and Exploratory Analysis

8.1. Pharmacokinetic Analysis

PK analyses will be described in separate analysis plans, and results will be reported outside the Clinical Study Report for the study.

8.2. Pharmacodynamic analyses

Secondary and exploratory PD variables (bile acids, C4, FGF-19, autotaxin, ProC3, hsCRP, MMP7, MMP9, ELF score, and CA 19-9) will be analyzed descriptively for categorical and continuous data, as applicable. For continuous data, the relative and absolute change from baseline 1 at each post-baseline visit will be analyzed in addition to the actual values. 2-sided 95% CI of the mean for relative and absolute change from baseline 1, and actual values will be

presented along with descriptive statistics. Similarly, summary tables presenting relative and absolute change from baseline 2 for the 12-week treatment period will be presented. For categorical data, shift tables or frequency and percentages of patients will be presented as appropriate.

8.2.1. Bile Acids

Individual and total serum and urine bile acids will be presented. The relative and absolute change from baseline 1 in individual and total serum bile acids parameters will be presented at visits in Table 1 . For serum bile acid parameters, baseline 1 is defined as the average of all Screening results and results on the day of the planned single dose if both results are available. Otherwise, baseline 1 will be defined as the last non-missing assessment prior to the study drug administration of planned single dose. Similarly, the relative and absolute change from baseline 1 in urine samples for individual and total bile acids parameters will be presented at visits in Table 2. For urine bile acid parameters, baseline 1 is defined as the last non-missing assessment of that parameter prior to the study drug administration of planned single dose.

The following bile acid parameters will be summarised in two units (µg/mL or µmol/L) if applicable:

- Observed individual serum bile acids
- Observed total serum bile acids (both central lab data and specialized vendor data will be presented)
- Calculated total serum bile acids without all UDCA bile acids, which is the sum of all individual serum bile acids excluding all UDCAs (UDCA, GUDCA, TUDCA)
- Calculated conjugated serum bile acids (GCA, GLCA, GDCA, GCDCA, GUDCA, TCA, TCDCA, TDCA, TLCA, TUDCA)
- Calculated unconjugated serum bile acids (CA, LCA, DCA, CDCA, UDCA)
- Observed individual urine bile acids
- Observed total urine bile acids
- Calculated total urine bile acids without all UDCA bile acids, which is the sum of all individual urine bile acids excluding all UDCAs (UDCA, GUDCA, UDCA-S, GUDCA-S)
- Calculated conjugated urine bile acids (GCA, GLCA, GDCA, GCDCA, GUDCA)
- Calculated unconjugated urine bile acids (CA, LCA, DCA, CDCA, UDCA)
- Calculated conjugated urine sulfated bile acids (GCA-S, GLCA-S, GDCA-S, GCDCA-S, GUDCA-S)
- Calculated unconjugated urine sulfated bile acids (CA-S, LCA-S, DCA-S, CDCA-S, UDCA-S)

Summary tables presenting the relative and absolute change from baseline 1 in urine bile acids amount will be presented at visits in Table 2. Urine bile acids amount will be calculated as follows:

Urine bile acid amount (µg) = Urine bile acid concentration under unit µg/mL × [(Urine weight (g)) / (Urine density)]. The density for Urine is 1.005 g/mL.
Urine bile acid amount (µmol) = Urine bile acid concentration under unit µmol/L × [(Urine weight (g)) / (Urine density)] ×0.001. The density for Urine is 1.005 g/mL.

The following urine bile acid amount parameters will be summarised in two units (µg and µmol):

- Individual Urine Bile Acid Amount
- Total Urine Bile Acid Amount
- Total Urine Bile Acid Amount without all UDCAs
- Conjugated Urine Bile Acids Amount
- Conjugated Urine Sulfated Bile Acids Amount
- Unconjugated Urine Bile Acids Amount
- Unconjugated Urine Sulfated Bile Acids Amount

Similar summary tables presenting relative and absolute change from baseline 2 for the 12-week treatment period will be presented for all above bile acid parameters for patients in the PD analysis set who actively entered the 12-Week treatment period. Baseline 2 for the 12-week treatment period is defined as the last non-missing value of the assessment prior to the 12-week treatment period (V3).

A listing of bile acid levels will be presented for the PD analysis set. For urine bile acid levels, urine sample collection duration will be included in the listing. It will be calculated under unit hour as follows:

Urine sample collection duration = (Collection End Datetime – Collection Start Datetime) / 3600.

8.2.2. Serum Biomarkers

Biomarkers of liver inflammation and fibrosis will be presented, including autotaxin, ProC3, hsCRP, MMP7, MMP9, ELF score, and CA 19-9. ELF individual factors (Procollagen 3, Hyaluronic Acid (HA), Tissue Inhibitor of Metalloproteinase 1 (TIMP1)) will be displayed along with ELF score. Bile acid synthesis biomarkers, C4 and FGF-19, will also be assessed. Relative and absolute change from baseline 1 for the serum biomarkers will be presented according to Table 2. Baseline 1 is defined as assessment performed on the day of the planned single dose.

Similar summary tables presenting relative and absolute change from baseline 2 for the 12-week treatment period will be presented for all above serum biomarker parameters for patients in the PD analysis set who actively entered the 12-Week treatment period. Baseline 2 for the 12-week treatment period is defined as the last non-missing value of the assessment prior to the 12-week treatment period (V3).

A listing of serum biomarker parameters will be presented for the PD analysis set.

9. Safety Analysis

Safety will be assessed through summaries of TEAEs, serious adverse events (SAEs), vital signs, ECGs, physical examinations, clinical laboratory tests (hematology, clinical chemistry, urinalysis, and coagulation), and concomitant medication. Analyses will be performed using the Safety Analysis Set.

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in an enrolled patient regardless of causal relationship with the study drug. An AE can therefore be any clinically significant unfavorable and unintended sign, symptom, or disease that occurs during the study, whether or not related to the study drug.
A TEAE in this study is defined as an AE occurring during the treatment period and within 14 days follow-up after the last dose that meets any of the following conditions:

- Any new AE that occurs on or after the first dose of study drug;
- An existing disease that occurs before the first dose of study drug, but worsens in severity on or after the first dose of study drug.

Adverse events will be coded using Version 28.0 of the MedDRA. The severity of AEs will be assessed by the investigator based on the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 grading system.

Summary of AEs will include.

- Overview of the incidence of TEAEs (TEAEs, TEAEs by Severity, Serious TEAEs, Drug-related TEAEs, Serious Drug-related TEAEs, Severe Drug-Related TEAEs, TEAEs leading to treatment discontinuation, Drug-related TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, Drug-related TEAEs leading to treatment interruption, TEAEs leading to study discontinuation, Drug-related TEAEs leading to study discontinuation, and TEAEs leading to death).
- TEAEs by SOC and PT.
- TEAEs by PT in Descending order of frequency.
- TEAEs by Severity, SOC and PT.
- Study Drug-related TEAEs by SOC and PT.
- Study Drug-related TEAEs by PT in Descending order of frequency.
- Study Drug-related TEAEs by Severity, SOC and PT.
- TEAEs leading to treatment discontinuation by SOC and PT.
- Study Drug-related TEAEs leading to treatment discontinuation by SOC and PT.
- TEAEs leading to treatment interruption by SOC and PT.
- Study Drug-related TEAEs leading to treatment interruption by SOC and PT.
- TEAEs leading to study discontinuation by SOC and PT.
- Study Drug-related TEAEs leading to study discontinuation by SOC and PT.
- Serious TEAEs by SOC and PT.

A patient with multiple AEs within a primary SOC or PT will only be counted once towards the total for that SOC and/or PT. For the AE severity and relationship summaries, if a patient reported more than one AE with the same PT, the AE with the greatest severity or relationship will be presented. For table summaries if severity is missing then ‘Grade 3 (Severe)’ is assumed. For the purposes of summarising AEs related to study drug, a relationship of ‘possibly related’, ‘probably related’ or ‘definitely related’ will be considered as related to the study drug. A relationship of ‘not related’ or ‘unlikely related’ will be considered as not related to the study drug. If relationship is missing, relationship to study drug is assumed to be ‘related’. AEs with a

toxicity grade of greater than or equal to grade 3 will be considered as severe adverse events. Summaries of TEAEs will be presented separately by the single dose (Day 1 to Day 14), 12-week (Day 15 to Day 112) and overall treatment periods by treatment arm and overall.

Following patient listings will be provided based on the safety analysis set.

- TEAEs
- SAEs
- Drug-related AEs
- AEs leading to treatment discontinuation
- AEs leading to treatment interruption
- AEs leading to study discontinuation
- Deaths

9.2. Clinical Laboratory Evaluations

Clinical safety laboratory evaluations will be performed by a central laboratory. Samples will be collected for clinical laboratory evaluations at timepoints indicated in Table 1 and Table 2. Safety lab parameter like clinical chemistry and urinalysis (Appendix 2) will be presented from Baseline up to Follow-Up after 12-Week Treatment. Hematology will be presented at Baseline, Start of 12-Week Treatment up to Follow-Up after 12-Week Treatment. Coagulation will be presented at Baseline, Start of 12-Week Treatment, Week 4 of 12-Week Treatment and Week 12 of 12-Week Treatment.

Descriptive statistics for clinical laboratory values [chemistry, hematology, urinalysis, coagulation laboratory tests, LBTs including aminotransferase (ALT and AST), GGT, ALP, and total and direct bilirubin levels] will be presented. For LBTs, 2-sided 95% CI of the mean for relative and absolute change from baseline 1 to each post-baseline visit and the last visit, and actual values at each visit will be presented along with descriptive statistics. Relative and absolute changes from baseline 1 to each post-baseline visit and the last visit will also be presented for quantitative variables. For clinical chemistry assessments and urinalysis tests with quantitative results, baseline 1 is defined as the average of all Screening results and results on the day of the planned single dose if both results are available. Otherwise, baseline 1 will be defined as the last non-missing assessment prior to the study drug administration of planned single dose. For other laboratory parameters, baseline 1 is defined as the last non-missing assessment of that parameter prior to the study drug administration of planned single dose. For categorical variables (i.e., normal or abnormal findings, or qualitative clinical laboratory tests), a table of categorical values over time will be presented. Results of quantitative clinical laboratory values will be categorized as low, normal, or high according to laboratory range specifications. Shifts from baseline 1 to each scheduled post-baseline time point will be presented to show the number and percentage of patients in each category by parameter.

Similar summary tables presenting relative and absolute change from baseline 2 to each post-baseline visit and the last visit for the 12-week treatment period will be presented for LBTs and chemistry and urinalysis laboratory quantitative variables for patients in the Safety Analysis Set who actively entered 12-Week treatment period. For the 12-week treatment period, similar shifts from baseline 2 summaries will be presented for chemistry laboratory parameters based on the

baseline 2 of 12-week treatment period for patients in the Safety Analysis Set who actively entered 12-Week treatment period. Baseline 2 for the 12-week treatment period is defined as the last non-missing value of the assessment prior to the 12-week treatment period (V3).

All laboratory data test results, laboratory toxicity and corresponding CTCAE grades will be included in data listings.

9.2.1. Suspected Drug-Induced Liver Injury

The number and percentage of patients with at least one post-baseline abnormal liver function test will be presented. A listing of patients who have abnormal liver function tests and meet DILI criteria will be provided, including the patient ID, visit, collection date, DILI parameters (ALT, AST, BILI, INR, LDH, CPK) and criteria. Abnormal liver function tests are defined as liver test values that meet at least one of the criteria listed below:

Liver Chemistries that trigger Drug-Induced Liver Injury (DILI) investigation:

- Transaminases (ALT or AST ≥ 3 x baseline or 500 U/L, whichever comes first) AND bilirubin (total bilirubin > 2 x ULN) elevations.
- Transaminase elevations alone (ALT or AST > 10 x ULN or 5 x baseline or absolute threshold of 800 U/L, whichever comes first) in the presence of normal LDH and CPK.
- Total bilirubin increased, unrelated to hemolysis (elevated reticulocyte count) or established genetic diseases, such as Gilbert's syndrome:
    - Doubling if total bilirubin was < 3 mg/dL (equivalent to 51.3 μmol/L) at baseline OR
    - Increase by > 3 mg/dL (equivalent to 51.3 μmol/L) if total bilirubin was ≥ 3 mg/dL (equivalent to 51.3 μmol/L) at baseline.
- INR increase refractory to vitamin K administration.
    - Increase by > 1.5 if INR was normal at baseline OR
    - Increase by > 0.4 if INR was abnormal at baseline.
- Any increase in total bilirubin and transaminases if accompanied by EITHER a symptom of clinical hepatitis (e.g., vomiting, nausea, right upper quadrant pain) OR immunological reaction (rash or > 5% eosinophilia)

Below six eDISH plots (maximum ALT/AST with concurrent TBL) will be presented:

- Total bilirubin (in xULN) versus maximum post-baseline ALT (in xULN) for participants with baseline ALT=<ULN;
- Total bilirubin (in xULN) versus maximum post-baseline AST (in xULN) for participants with baseline AST=<ULN;
- Total bilirubin (in xBaseline) versus maximum post-baseline ALT (in xBaseline) for participants with baseline ALT>ULN;
- Total bilirubin (in xBaseline) versus maximum post-baseline AST (in xBaseline) for participants with baseline AST>ULN;
- Total bilirubin (in xULN) versus maximum post-baseline ALT (in xBaseline) for participants with baseline ALT>ULN;

- Total bilirubin (in xULN) versus maximum post-baseline AST (in xBaseline) for participants with baseline AST>ULN

The individual graphs (ALT, AST, TBL, and ALP) (xULN vs Study Days) for any participants meeting the DILI criteria or participants with TEAEs related to ALT/AST and other Hepatic Enzyme Elevations will be presented. Study day based on the date of planned single dose will be used.

9.2.2. Faecal Calprotectin Assessment

For patients with IBD, stool samples will be collected (at home) prior to each study visit for assessment of faecal calprotectin. Faecal calprotectin assessments are performed at visits indicated in Table 2.

Summary table of observed values, relative and absolute change from baseline 1 to each post-baseline visit and the last visit will be presented in the Safety analysis set. The 2-sided 95% CI of the mean for relative and absolute change from baseline 1, and observed values will be presented along with descriptive statistics. Baseline 1 is defined as assessment performed on the day of the planned single dose. Supporting listing will also be presented for the Safety Analysis Set.

9.3. Vital Sign Measurements

Summary tables will be presented by treatment for vital sign data, including height (cm), weight (kg), pulse rate (PR) (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and temperature (°C) in the Safety analysis set. Observed results and absolute change from baseline 1 to each post-baseline time point and the last visit will be presented. Change from baseline 1 will only be calculated for patients having non-missing baseline 1 and post-baseline measurements. The height assessment will only be done at the Screening visit. All vital signs data will be presented in a listing.

Abnormal vital sign values are defined as post-baseline values that meet one of the criteria listed below if baseline 1 values are normal, or post-baseline values that worse than the baseline value if baseline 1 values are abnormal. The number and percentage of patients with at least one post-baseline abnormal vital sign value will be presented. The shift table in categories (Low, Normal, High) for the minimum and maximum post baseline values will be presented for each vital sign parameter. This will also be repeated for each timepoint according to the Schedule of Assessment. A supportive listing of patients with abnormal post-baseline values will be provided including the patient ID, baseline 1, post-baseline values and criteria.
Abnormal vital sign values will be presented based on the following criteria:

- Systolic blood pressure (mmHg):
  - Normal - ≥ 90 and ≤ 140
  - Low - < 90
  - High - > 140
- Diastolic blood pressure (mmHg):
  - Normal - ≥ 50 and ≤ 90
  - Low - < 50
  - High - > 90
- Pulse rate(beats/min):

- Normal - ≥ 50 and ≤ 120
- Low - < 50
- High - > 120

9.4. Physical examination

A physician or suitably trained qualified assistant will perform a complete physical examination at times presented in Table 2. A complete physical examination will include assessment of general appearance, eyes, ears, nose, throat, head/neck/thyroid, lymph nodes, cardiovascular, lungs/chest, abdomen, genitourinary, extremities, skin, musculoskeletal, and neurologic system; any other findings will also be documented.
Physical examination results will be summarised at each visit with percentages and frequencies along with abnormalities by treatment arm. Physical examination and skin assessment data will be listed (including pre-treatment and post-treatment results).

9.5. Electrocardiogram results

Standard resting 12-lead electrocardiograms (ECGs) will be recorded after the patient has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments and when judged to be clinically appropriate. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG. The PR, RR, QT and QTcF intervals; QRS duration; and heart rate will be presented.

An overall 12-lead ECG interpretation (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) will be available based on central reading of ECG data. Shifts from baseline 1 to each scheduled post-baseline time point will be presented to show the number and percentage of patients in each category by treatment for patients in the Safety Analysis Set.

A shift table for ECG interpretation will present the shift from baseline 1 to each post-baseline assessment. Patients will be summarised by treatment arms.

Descriptive statistics for observed values at each time point and absolute changes from baseline 1 will be summarised for heart rate (beats/min), PR interval (msec), RR Interval (msec), QRS duration (msec), QT interval (msec), corrected QT interval based on Fridericia's formula (QTcF) (msec) at each scheduled visit. ECG interpretation results (normal; abnormal not clinically significant; abnormal clinically significant) will be presented as the number and percentage of patients in each category at scheduled visits. Patients will be summarised by treatment arm.

All ECG results will be presented in a listing.

9.6. Episodes of cholangitis requiring Antibiotic use

A summary table of the patients with episodes of cholangitis requiring antibiotic use in the 12 weeks prior to single dosing versus the 12-week treatment period will be presented for the Safety Analysis Set. Baseline 1 is defined as data collected on the day of the planned single dose, which are assessments of 12 weeks prior to Single Dosing. Supporting listing will also be presented for the Safety Analysis Set.

9.7. MELD Score

For Arm 4, the MELD score will be calculated as follows:

MELD Score = 9.57 × ln (creatinine mg/dL) + 3.78 × ln (total bilirubin mg/dL) + 11.2 × ln (INR) + 6.43

The MELD Na Score will be calculated as follows:

MELD Na Score = MELD − Na (mEq/L) − [0.025 × MELD × (140 − Na (mEq/L))] + 140

For calculation of the MELD score, laboratory values less than 1.0 will be set to 1.0 and serum creatinine values greater than 4.0 mg/dL (equivalent to 353.6 µmol/L) will be set to 4.0. For calculation of the MELD Na score, sodium (Na) values greater than 140 mEq/L will be set to 140 and values less than 125 mEq/L will be set to 125.
For Arm 4, absolute change from baseline 1 in MELD score will be presented for the Safety Analysis Set. Similar summary tables presenting absolute change from baseline 2 for the 12-week treatment period will be presented for MELD scores for patients in the Safety Analysis Set who actively entered 12-Week treatment period. Supporting listing will also be presented for the Safety Analysis Set.

9.8. Endoscopic biliary dilation intervals/frequency

For Arm 4, a summary table of endoscopic biliary dilation intervals/frequency will be presented for the Safety Analysis Set. The absolute and relative change in the 12 weeks prior to single dosing (V2) compared to the 12-week treatment period (V7) table will also be presented for the Safety Analysis Set. Baseline 1 is defined as data collected on the day of the planned single dose, which are assessments of 12 weeks prior to Single Dosing. Supporting listing will also be presented for the Safety Analysis Set.

9.9. Liver stiffness

Liver stiffness will be assessed by FibroScan. Fibroscan will be performed as per institution standard practice where available. The data collected on the Fibroscan form (liver stiffness measured in kPa) will be converted to determine stage of fibrosis on a 0 to 4 scale, using below score card based on grading from the study that looked at liver stiffness measurements (LSM) and association with degree of fibrosis in patients with PSC (Corpechot 2014) as outlined in Table 3.

Table 3: Fibroscan Scoring (Fibrosis Stage)

STAGE	F0 NO FIBROSIS	F1 PORTAL FIBROSIS WITHOUT SEPTA	F2 PORTAL AND PERIPORTAL FIBROSIS WITH FEW SEPTA	F3 PORTAL AND PERIPORTAL FIBROSIS WITH NUMEROUS SEPTA WITHOUT CIRRHOSIS	F4 CIRRHOSIS
Liver stiffness measurement by Fibroscan	<7.4 kPa	≥7.4 to <8.6 kPa	≥8.6 to <9.6 kPa	≥9.6 to <14.4 kPa	≥14.4 kPa

Relative and absolute change from baseline 1 in Fibroscan results will be presented for the Safety Analysis Set. Similar summary tables presenting relative and absolute change from baseline 2 for the 12-week treatment period will be presented for Fibroscan results for patients in the Safety Analysis Set who actively entered 12-Week treatment period. A listing of liver stiffness will also be presented for the Safety Analysis Set. The frequencies of stages may be summarised by frequency tables.

9.10. Mayo PSC-score

The Mayo PSC score will be calculated as follow:

$R = 0.03$ (age [y]) + $0.54 \log_e$ (bilirubin [mg/dL]) + $0.54 \log_e$ (aspartate aminotransferase [U/L]) + 1.24 (variceal bleeding [0/1]) – 0.84 (albumin [g/dL]).

Where R is the Risk Score.

Absolute change from baseline 1 in Mayo PSC Score will be presented for the Safety Analysis Set. Similar summary tables presenting absolute change from baseline 2 for the 12-week treatment period will be presented for Mayo PSC Score for patients in the Safety Analysis Set who actively entered 12-Week treatment period. A listing of Mayo PSC Score will also be presented for the Safety Analysis Set.

9.11. Numerical Rating Score Assessments

The scoring of NRS will range from 0 (“No itch”) to 10 (“worst imaginable itch”). This will be interpreted as follows:

- NRS = 0 – No Pruritus
- NRS < 3 – Mild Pruritus
- NRS ≥ 3<7 – Moderate Pruritus
- NRS ≥ 7<9 – Severe Pruritus
- NRS ≥ 9 – Very Severe Pruritus

These scores will be used for Pruritus, Fatigue and Sleep Disturbance.

For Patient Diary Reviews (Pruritus NRS, Fatigue NRS, Sleep Disturbance NRS, Mood Likert Scale), the weekly, biweekly and monthly score will be calculated as in Appendix 3 based on each period. The following assessments will be presented at each weekly, biweekly and monthly period. Baseline 1 will be calculated by averaging the two-baseline weekly score in the 14 days preceding the planned single dose. The single treatment period score is calculated by averaging the weekly scores in the 14 days of single treatment period of planned single dose. For biweekly and monthly score summary, single treatment period of planned single dose will be included as the first post-baseline period; 2-week safety follow-up period will be presented as the last post-baseline period.

9.11.1. Daily Pruritus Score

Pruritus NRS will be completed in the patient diary only for patients that report experiencing pruritus at the Screening Visit. The summary table and relative and absolute change from baseline 1 in pruritus derived using the Pruritus NRS will be presented for the Safety Analysis Set. A listing of daily pruritus score will also be presented for the Safety Analysis Set.

9.11.2. Fatigue Score

The summary table and relative and absolute change from baseline 1 in fatigue score derived using the Fatigue NRS will be presented for the Safety Analysis Set. A listing of Fatigue score will also be presented for the Safety Analysis Set.

9.11.3. Sleep disturbance Score

The summary table and relative and absolute change from baseline 1 in sleep disturbance score derived using the sleep disturbance NRS will be presented for the Safety Analysis Set. A listing of sleep disturbance score will also be presented for the Safety Analysis Set.

9.11.4. Mood Scale

Mood Likert scale data collected in the patient diary will be converted to numerical scores using below criteria:

- Never – 0
- Almost never – 1
- Sometimes – 2
- Often – 3
- Always – 4

The summary table of mood Likert scales and relative and absolute change from baseline 1 in mood scores using above criteria will be presented for the Safety Analysis Set. A listing of mood scales will also be presented for the Safety Analysis Set.

9.12. Pregnancy

Serum pregnancy test will be performed for all women upon Screening. For women of childbearing potential (WOCBP), urine pregnancy test will be done at Visit 2 through Visit 8. A point of care urine dipstick for pregnancy will be obtained. If the results are positive for pregnancy, a human chorionic gonadotropin (hCG) blood pregnancy test will be performed. A Patient listing of pregnancy test results will be provided.

10. Interim Analysis/Other Analysis

10.1. Interim Analysis

An interim analysis may be conducted. This analysis will be triggered by ongoing review of data and need for communication with regulatory authorities/agencies. Additional analyses may be performed at selected time points throughout the collection of patient data for regulatory requirements and sponsor decision making purposes.

10.2. Safety Review Committee

An SRC will be established for Study A3907-002 which may consist of the sponsor, and the lead investigator (as detailed in the SRC charter). The SRC will review safety and PK data after at least three (3) patients have completed two (2) weeks of treatment in Arm 1 to determine if enrolment in Arm 2 may occur. The SRC will review safety and PK data after at least three (3) patients have completed two (2) weeks of treatment in Arm 2 to determine if enrolment in Arms 3 and 4 may occur. The SRC will also meet periodically for the review of accumulating study data, including safety (AE and laboratory data), until the last patient reaches 12 weeks.

The SRC will make recommendations for the remaining part of the study. The SRC may recommend continuing with the study as planned or stopping the study early for safety reasons. The investigators (or designees) will only be informed by the sponsor or designee if the study requires a protocol amendment or is stopped. The SRC may choose to make additional evaluations at any time if they feel this is warranted from a safety point of view.

10.3. Coronavirus Pandemic

In accordance with guidance issued by regulatory agencies, study data collection will document visits missed due to COVID-19 related reasons and assessments completed via alternative method due to COVID-19 related reasons.

The COVID-19 impacts on individual patients collected on the COVID-19 eCRF pages will be listed for the Enrolled Set. Protocol deviations related to COVID-19 will be indicated in the protocol deviation listing for the Enrolled Set.

The anticipated impact of COVID-19 is widely regarded as unknown. If the impact of COVID-19 on the conduct of this study is observed to be significant, further summaries and listings of the impact will be explored.

11. Changes in the Planned Analysis from Study Protocol section

Day 0 in the protocol has been updated to Day 1 in SAP.
The protocol contains different statistical analysis sets, Screened Set and Enrolled Set were added in the SAP to support disposition analysis and supporting listings.
MIST analysis will not be conducted.
Laboratory clinical significance determined by the investigator’s discretion is not available and will not be presented in the analysis. However, laboratory toxicity and its CTCAE grades will be included in the listings.

12. Reference

Corpechot C, Gaouar F, El Naggar A, Kemgang A, Wendum D, Poupon R, Carrat F, Chazouillères O. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. Gastroenterology. 2014 Apr;146(4):970-9; quiz e15-6. doi: 10.1053/j.gastro.2013.12.030. Epub 2013 Dec 31. PMID: 24389304.

13. Appendices

13.1. Appendix 1: Imputation Algorithm for Partial and Missing Dates

13.1.1. Rules for AE Start Date Imputation

The following rules will be applied to impute the missing numerical fields.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug and the end date is on or after the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.
- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug and the end date is prior to the first dose of study drug, then 01 January will be assigned to the missing fields.
- If the year of the incomplete start date is different from the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug and the end date is on or after the first dose of study drug, then the day of the date of the first dose of study drug will be assigned to the missing day.
- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug and the end date is prior to the first dose of study drug, then the first day of the month will be assigned to the missing day.
- If the month and year are different from the year of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

Missing year

- If the year of AE start is missing or AE start date is completely missing, then query the site with no imputation.

13.1.2. Rules for AE End Date Imputation

Incomplete stop dates will not be imputed.

13.1.3. Rules for Non-Study Medication Start Date Imputation

The following rules will be applied to impute the missing numerical fields. If the imputed start date is after the imputed stop date, then the start date will be imputed using the stop date.

Missing day and month

- 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- The first day of the month will be assigned to the missing day.

Missing year

- If the year is missing or start date is completely missing, then the date of the first dose of study drug will be assigned to the missing fields.

13.1.4. Rules for Non-Study Medication end Date Imputation

The following rules will be applied to impute the missing numerical fields. Imputation of medication end date must be done before imputation of medication start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of the date of the last contact date, then the day and month of the date of the last contact date will be assigned to the missing fields.
- Otherwise, 31 December will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last contact date, then the day of the date of the last contact date will be assigned to the missing day.
- Otherwise, the last day of the month will be assigned to the missing day.

Any imputed stop date that is after the date of death will be set to the date of death.

13.2. Appendix 2: Laboratory parameters

Clinical Chemistry	Hematology	Urinalysis
• Albumin	• Haematocrit • Haemoglobin	• Blood • Glucose

<table>
<tr><th>Clinical Chemistry</th><th>Hematology</th><th>Urinalysis</th></tr>
<tr>
<td rowspan="2">• Alanine aminotransferase (ALT)
• Alkaline phosphatase (ALP)*
• Aspartate aminotransferase (AST)
• Bilirubin – total and conjugated.
• Calcium
• Chloride
• Creatinine
• Creatine phosphokinase
• Gamma-glutamyl transferase (GGT)
• Lactate dehydrogenase
• Potassium
• Sodium
• Low-density lipoprotein cholesterol (LDL-C)</td>
<td>• Platelet count
• Red blood cell count
• White blood cell count and differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)</td>
<td rowspan="2">• Ketones
• Leukocytes
• Nitrites
• pH
• Protein
• Oxalate</td>
</tr>
<tr>
<td>Coagulation
• Prothrombin time
• Activated partial thromboplastin time.
• Thrombin time
• Prothrombin International Normalized Ratio (INR)</td>
</tr>
</table>

13.3. Appendix 3: Derived Variables for Patient Diary

The Patient Diary will be completed daily and collected at each study visit. Pruritus NRS will be completed in the patient diary only for patients that report experiencing pruritus at the Screening Visit. Diary compliance review to be performed at Visit 2 to Visit 8.

The table below provides the list of derived variables for duration derivations, drug exposure and compliance, baseline, weekly or monthly pruritus NRS and/or fatigue NRS, sleep disturbance NRS, and mood Likert scale derivations for this study.

Variables	Formula
Derivation of Duration	
Study day at any visit	Date of interest – Date of first dose of study drug. One day is added if this difference is ≥ 0.
Study day compared to the date of the planned single dose	Date of interest – Date of the planned single dose. One day is added if this difference is ≥ 0.
Extent of Exposure	
Duration of treatment exposure for 12-week treatment period (days)	Date of last study drug intake – Date of first study drug intake during 12-week treatment period +1.
Overall Study Drug Compliance	
Compliance for 12-week treatment period	100 × sum of (number of tablets actually taken during 12-week treatment period) / sum of (number of tablets planned to be taken per day * dose duration of 12-week treatment period under this planned dose amount).
Derivation for Patient Diary Parameters	
Baseline score (weekly, biweekly, or monthly) for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	The baseline is calculated by averaging the two-baseline weekly scores in the 14 days preceding the planned single dose. Baseline score will be unrounded. Baseline values can only be calculated if both weeks can be calculated. If weekly score is not available, the baseline is calculated by averaging all the daily scores

Variables	Formula
	if at least 7 daily scores available. Otherwise, baseline is considered as missing.
Weekly score for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	The weekly score is calculated by averaging the daily scores in a week. Each week, at least 4 of 7 daily scores need to be collected to calculate the weekly score (i.e., 50% rule). If these minimum assessments are not available, the weekly score is considered missing. Regarding the weekly period of the weekly patient diary scores, the 2 weeks between Study Day* -13 and Study Day* 1 will be considered as the 2 weeks before the planned single dose, and the 2 weeks between Study Day* 2 and Study Day* 15 will be considered for the single dose period. (*Study day compared to the date of the planned single dose will be used here.) For the 12-week treatment period, the first 12 weeks following the initial day of 12-week treatment will be considered. Additionally, for the safety follow-up period, the first 2 weeks following first day of safety follow-up period will be considered.
Single treatment period score for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	The single treatment period score is calculated by averaging the weekly scores in the 14 days of single treatment period of planned single dose. It will be unrounded. It can only be calculated if both weeks can be calculated. If weekly score is not available, the single treatment period score is calculated by averaging all the daily scores if at least 7 daily scores available. Otherwise, it is considered as missing. Single treatment period score will be included in both bi-week and monthly analysis.
Safety Follow-Up period score for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	The safety follow-up period score is calculated by averaging the weekly scores in the 14 days of safety follow-up period. It will be unrounded. It can only be calculated if both weeks can be calculated. If weekly score is not available, safety follow-up period score is calculated by averaging all the daily scores if at least 7 daily scores available. Otherwise, it is considered as missing.
Biweekly score for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	12-week treatment period biweekly (14 days) score is calculated by averaging the weekly scores in the two weeks of the biweekly period. It can only be calculated if both weeks can be calculated. If weekly score is not available, the post-single dosing biweekly score is calculated by averaging all the daily scores if at least 7 daily scores available. Otherwise, it is considered as missing.

Variables	Formula
Monthly score for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	The 12-week treatment period monthly (28 days) score is calculated by averaging 4 weekly scores within the 4-week interval. The monthly score can only be calculated if at least 3 of 4 weekly scores within the 4-week interval can be calculated.
Change from baseline for pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale	The weekly, biweekly, and monthly score change from baseline is calculated by subtracting the baseline score from the weekly, biweekly and monthly score.
Urine Sample Collection	
Duration of urine sample collection (hours)	(Collection End Datetime – Collection Start Datetime) / 3600.