CLINICAL STUDY PROTOCOL 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)

EU CT number:	2022-500790-14-00
Test Product:	A3907
Alternative Test Product Name:	IPN60250
Indication:	Primary Sclerosing Cholangitis
Sponsor:	Albireo AB
Development Phase:	2
Sponsor Signatory:	**PPD**
Date of the Protocol:	14 July 2023
Version of the Protocol:	3.0

Confidential

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: 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)

PROTOCOL NUMBER: A3907-002

Albireo AB

PPD

17 July 2023 | 08:24 EDT

Date (ddMMMyyyy)

Medical Director, Clinical Development
Albireo AB

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: 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)

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I have read this protocol and agree that it contains all necessary details for performing this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP), local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

I will use only the informed consent approved by the Independent Ethics Committee (IEC) and will fulfil all responsibilities for submitting pertinent information to the IEC responsible for this study.

I agree that the Sponsor (Albireo AB) shall have access to any source documents from which case report form information may have been generated.

I further agree not to originate or use the name of Albireo AB or A3907 in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment to the protocol, or to the performance of this protocol without the prior written consent of Albireo AB.

_____

Name of Investigator

_____ _____

Signature Date (ddMMMyyyy)

1 ADMINISTRATIVE INFORMATION

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)

Protocol No.:	A3907-002
Date of the Initial Protocol:	28JUN2022
Date and Number of Amendment(s):	Amendment 1, 15NOV2022 Amendment 2, 07 July 2023
Sponsor:	Albireo AB Arvid Wallgrens Backe 20 413 46 Göteborg Sweden
Clinical Research Organization:	CCI
Sponsor Signatory:	**PPD** Medical Director, Clinical Development Albireo AB Arvid Wallgrens Backe 20 413 46 Göteborg Sweden

2 STUDY SYNOPSIS

Name of Sponsor/Company: Albireo AB	**Name of Product:** A3907	**Name of Active Ingredient:** A3907
Title of Study: 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)		
Study Centres: Up to 7 in Europe		
Publication(s): None		
Planned Study Period: 2022-2025	**Development Phase:** Phase 2	

Objectives and Endpoints

	Objective	**Endpoint**
Primary	To evaluate the safety and tolerability of A3907 in patients with PSC with and without a Clinically Relevant Stricture (CRS) following repeat doses.	Incidence of treatment-emergent adverse events (TEAEs) through Week 12
Secondary	To evaluate the pharmacokinetics (PK) of A3907	PK parameters for A3907 including, but not limited to, maximum observed plasma concentration (Cmax), and area under the plasma concentration time curve (AUC)
	To evaluate the effect of A3907 on bile acid levels	Change from Baseline to Week 12 in serum, urine and individual and total bile acid levels
	To evaluate the effect of A3907 on liver health	Change from Baseline to Week 12 in LBTs: aminotransferases (ALT and AST), gamma-glutamyl transferase (GGT), ALP, and total and direct bilirubin levels.
	To evaluate the effect of A3907 on bile acid synthesis	Change from Baseline to Week 12 in 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF-19)

Name of Sponsor/Company: Albireo AB	Name of Product: A3907	Name of Active Ingredient: A3907
Exploratory	To explore the effect of A3907 on markers of liver inflammation and fibrosis	• 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 (MMP) 7 and MMP9 • Change from Baseline to Week 12 in enhanced liver fibrosis (ELF) and Mayo-PSC score • Change from Baseline to Week 12 in CA 19-9 • Change from Baseline to Week 12 in liver stiffness as assessed by FibroScan
	To evaluate the effect of A3907 on symptoms	• Change 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
	To explore the effect of A3907 on episodes of cholangitis (for patients with available 12-week data prior to dosing)	Episodes of cholangitis requiring antibiotic use in the 12 weeks prior to dosing versus the 12 weeks after dosing

Name of Sponsor/Company: Albireo AB	Name of Product: A3907	Name of Active Ingredient: A3907
Exploratory Arm 4 Only	To evaluate the effects of A3907 on survival without a liver transplant	Change of MELD score from baseline to Week 12
	To evaluate the effect of A3907 on bile duct function	Change in endoscopic biliary dilation intervals/ frequency in the 12 weeks prior to study start (V2) compared to the 12--week treatment period for those subjects who are regularly dilated.

Methodology:

This is an open-label, Phase 2 study to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effects of 3 dose levels of A3907 (10 mg once daily [QD], 30 mg QD and 30mg twice daily [BID] administered orally for 12 weeks) in patients with PSC with and without a CRS.

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, and an End of Study Visit 14 days after the last dose of study drug.

There will be a total of 8 scheduled visits during the study (including 1 Screening Visit).

The study will have four arms as follows:

- Arm 1: patients with PSC dosed with 10mg QD
- Arm 2: patients with PSC dosed with 30mg QD
- Arm 3: patients with PSC dosed with 30mg BID
- Arm 4: patients with PSC who have a CRS dosed with 30mg BID

On Day 0, patients will receive a single daily dose of A3907 (10 mg QD [Arm 1], 30 mg QD [Arm 2], 30 mg BID [Arms 3 and 4]). Before each patient can begin the 12-week Treatment Period, individual PK evaluations will be conducted to ensure study drug exposure does not exceed the safety margin described in Section 5.4. If the exposures (C_{max} and AUC) exceed the highest systemic exposure as determined by the single ascending dose (SAD) data from the first in human (FIH) study, the individual patient will be terminated early.

Staggered Arms

Enrollment into treatment arms will be staggered as follows:

- Arm 2 will begin 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;
- Arms 3 and 4 will begin after at least 3 patients in Arm 2 have completed 2 weeks of treatment and the SRC has reviewed safety and PK data. Enrollment into Arm 4 will occur concurrently with Arm 3.

Safety Review Committee (SRC)

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Albireo AB	A3907	A3907

Study data will be reviewed by the SRC at regularly scheduled meetings, as described in the SRC charter. The SRC may convene ad-hoc meetings as necessary. The SRC may also review data from an optional interim analysis.

Last Dose

The last dose of study drug will be administered at 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-Study procedures within 14 days after the last dose of study drug.

Number of Patients:

Approximately 24 patients

Diagnosis and Criteria for Inclusion:

1. Adults between 18 and 75 years of age (inclusive).
2. Have a clinical diagnosis of large-duct PSC with evidence of more than 6 months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis and historical evidence of elevated alkaline phosphatase (ALP).
3. Willing to sign informed consent.
4. Women of childbearing potential (WOCBP) and males with female partners of childbearing potential must agree to use contraception as detailed in Section 9.3.18. Women of nonchildbearing potential (WONCBP) must meet the definition in Section 9.3.18 and have a confirmatory follicle-stimulating hormone [FSH] level ≥ 40 mIU/mL .
5. Alkaline Phosphatase (ALP) value > 1.5 × upper limit of normal (ULN) but ≤ 10 ×ULN at Visit 1 (Screening Period). Before starting 12 weeks treatment variability of < 30% between ALP values at Visit 1 and Visit 2 must be confirmed. If variability is > 30 % a third ALP value may be obtained. If the third ALP value meets >1.5 × ULN but ≤ 10 × ULN the patient can start the 12-week treatment period.
6. Arms 1-3 Only: Total bilirubin < 1.5 × ULN (unless due to Gilberts Syndrome or hemolysis) and normal direct bilirubin.
7. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × ULN
8. Serum bile acid level > ULN
9. Arms 1 - 3 Only: An MRCP or equivalent imaging modality performed within 6 months before the Screening Period that is consistent with PSC without a clinically relevant stricture.
10. Arm 4 Only: An MRCP or equivalent imaging modality performed within 6 months before the Screening Period that is consistent with PSC with a clinically relevant stricture, or clinically relevant bile duct obstruction (see Inclusion # 12 for additional information).
11. Use of ursodeoxycholic acid (UDCA) with a total daily dose ≤ 23 mg/kg/day, or bile acid-binding resins are permitted, with a minimum of 3 months of stable treatment prior to the Screening Period, and expected to remain on a stable dose through the 12-week treatment period; or a minimum of 3 months off UDCA prior to the Screening Period if UDCA was recently discontinued.
12. If a patient has inflammatory bowel disease (IBD) with a minimum disease duration of 4 weeks, this diagnosis should be documented. Inflammatory bowel disease should be in clinical remission or mildly active according to Crohn's Disease Activity Index (CDAI), partial Mayo score for Crohn's Disease (CD) and ulcerative colitis (UC), respectively (i.e. patients with CDAI score < 220 and

Name of Sponsor/Company:	Name of Product:	Name of Active Ingredient:
Albireo AB	A3907	A3907

Mayo score < 5, respectively). Patients with IBD should have had a colonoscopy performed within one year prior to the Screening Period with results showing no evidence of dysplasia or cancer.

13. Clinically stable for at least 3 months prior to the Screening Period.
14. Arm 4 Only: One stable clinically relevant biliary stricture of at least 4 weeks duration on contrast-enhanced MRI/MRCP with > 75% reduction of duct diameter in the common bile duct or hepatic duct without suspicion of cholangiocarcinoma (further established by imaging and stable CA 19-9 below ULN repeated twice over 1 month), or cholelithiasis. Subjects may have signs or symptoms of worsening obstructive cholestasis (increasing jaundice, nausea, anorexia, steatorrhea and worsening or new onset pruritus), deterioration of liver function (i.e. decreasing platelet count, increasing international normalized ratio [INR]) and/could be listed for liver transplantation due to their clinically relevant biliary stricture.
15. Arm 4 Only: MELD Score < 35

Main Criteria for Exclusion:

Medical History

1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis).
2. Arm 1-3 Only: Biliary intervention within 3 months prior to study enrollment or planned.
3. Arm 4 Only: Planned Biliary intervention between the Screening Period and baseline.
4. Presence of alternative causes of chronic liver disease, including alcohol-associated liver disease, nonalcoholic steatohepatitis, primary biliary cholangitis, autoimmune hepatitis, or active hepatitis B or C.
5. IBD with uncontrolled moderate to severe activity and/or on treatment with any immunosuppressive, immunomodulator, or biologic agent for treatment of IBD (i.e. azathioprine, 6 mercaptopurine, tacrolimus, methotrexate, infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, ozanimod). Treatment with corticosteroids (including budesonide, budesonide MMX and beclomethasone) in the previous 4 weeks.
6. History of human immunodeficiency virus infection or any other known relevant infection (e.g. tuberculosis).
7. History of ileectomy, colostomy or colectomy.
8. History of malignancy, including hepatocellular carcinoma and cholangiocarcinoma within the past 10 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
9. Alpha-fetoprotein (AFP) > 20 ng/mL (at the Screening Visit) with 4-phase liver CT or MRI suggesting presence of liver cancer.
10. History of transplants, including liver transplantation, or currently on active transplantation list (Arms 1-3). Arm 4 may be on an active liver transplantation list.
11. Current or a history of hepatic decompensation events including, but not limited to ascites, encephalopathy, or history of esophageal variceal bleeding.
12. Known or suspected overlapping clinical and histologic diagnosis of autoimmune hepatitis.

Name of Sponsor/Company:	Name of Product:	Name of Active Ingredient:
Albireo AB	A3907	A3907

13. Small duct PSC (evidence of PSC on historical liver histology, with normal bile ducts on cholangiography) without large duct PSC.
14. Liver cirrhosis as assessed by any of the following:
    a. historical liver histology.
    b. liver stiffness measurement, assessed by FibroScan (FibroScan value > 14.4 kPa), in addition to clinical assessment and biochemical markers at the discretion of the investigator.
    c. signs and symptoms of hepatic decompensation (including, but not limited to, jaundice, ascites, variceal haemorrhage, and/or hepatic encephalopathy).
15. History of bacterial cholangitis within 60 days prior to the Screening Period, or if the patient is on antibiotics for prophylaxis of recurrent cholangitis.
16. Females who are pregnant, lactating, or breast feeding as detailed in Section 9.3.18.
17. History of alcohol or substance abuse in the previous 2 years. Patients must agree to refrain from illicit drug (including marijuana) and alcohol use during the study.
18. Hypersensitivity to investigational medicinal product (A3907) and its excipients.
19. Presence of any contraindication for undergoing MRCP (e.g. pacemaker).
20. Any other condition or abnormality which, in the opinion of the investigator (or designee), may compromise the safety of the patient or interfere with the patient participating in, or completing the study.

Treatment Exclusions:

21. Administration of medications that slow gastrointestinal motility (Section 8.6.2).
22. Treatment with rifampicin.
23. Exposure to oral drugs that are strong inhibitors or inducers of CYP3A4 enzymes (e.g. grapefruit juice, ritonavir, itraconazole, ketoconazole, troleandomycin, rifampin, St John's wort, etc.) within 14 days prior to the Screening Period, or 5 half-lives of the drug, whichever is longer (Section 8.6.2).
24. Exposure to oral drugs that are substrates of CYP3A4 enzymes (e.g. codeine, ciclosporin [cyclosporin], diazepam, etc.) during the study (Section 8.6.2).
25. Treatment with vitamin D or fibrates, unless patient is on a stable dose ≥ 6 months prior to baseline.
26. Exposure to an investigational drug, biologic agent, or medical device within 30 days prior to the Screening Period, or 5 half-lives of the study agent, whichever is longer.

Laboratory Exclusions

27. Platelet count < 150 000/mm^3.
28. Albumin level < 3.0 g/dL.
29. INR > 1.3 (the patient may be treated with vitamin K intravenously, and if INR is ≤ 1.3 at resampling, the patient may be enrolled).
30. Medical conditions that may cause non-hepatic increases in ALP (e.g. Paget's disease). A GGT or ALP isoenzymes should be obtained for confirmation of biliary origin;
31. Glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2

Test Product, Dose and Mode of Administration:
A3907, 10 or 30 mg QD or 30 mg BID orally administered

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Reference Therapy, Dose and Duration of Administration: None		
Duration of Treatment: One day plus 12 weeks		

Statistical Methods:

Sample Size Considerations:

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. Approximately 24 patients are planned to be enrolled into the study.

Analysis Populations:

Safety Analysis Set

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

Pharmacokinetic Analysis Set

The PK analysis set will include all patients who received at least 1 dose of A3907 and have evaluable PK data. The PK analysis set will be used for all PK analyses.

Pharmacodynamic Analysis Set

The PD population will include all patients who received at least 1 dose of A3907 and for whom at least 1 PD marker can be evaluated. The PD analysis set will be used for all PD analyses.

Evaluation of Safety Variables:

Descriptive statistics will mainly be used in this open-label study. All statistical analyses will be performed using SAS version 9.3 or higher.

Safety data will be analyzed using descriptive statistics and overall summaries of adverse events (AEs), serious adverse events (SAEs), ECG, vital signs, clinical laboratory tests (haematology, clinical chemistry, urinalysis, and coagulation), and concomitant medication.

Evaluation of Pharmacokinetic Variables:

The PK analysis will be conducted by employing noncompartmental methods using WinNonlin®. Only patients who are given A3907 and have evaluable plasma concentration-time profiles will be included in the analysis.

Individual A3907 plasma concentrations at specified timepoints will be listed for each patient and will be summarised by dose level. Individual plasma concentration-time profiles of A3907 will be plotted on both a linear and a semi-logarithmic scale for each dose level. Mean values will also be presented graphically for each dose level.

Evaluation of Pharmacodynamic Variables:

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 change from baseline will be analyzed in addition to the actual visit values. For categorical data, shift tables or frequency and percentages of patients will be presented as appropriate.

An interim analysis may be performed.

Date of the Protocol: 14 July 2023

3 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Figures

3.3 List of Appendices and Supplements

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AFP	alpha-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASBT	apical sodium bile acid transporter
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BID	twice daily
C4	7α-hydroxy-4-cholesten-3-one
CA 19-9	carbohydrate antigen 19-9
CCA	cholangiocarcinoma
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRA	Clinical research associate
CRS	Clinically Relevant Stricture
CT	computerized tomography
ECG	electrocardiogram
eCRF	electronic case report form
ELF	enhanced liver fibrosis
ERCP	endoscopic retrograde cholangiopancreatography
EU	European Union
FDA	Food and Drug Administration
FIH	first-in-human
FGF-19	fibroblast growth factor 19
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
hsCRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalised ratio
IRB	International Review Board
IXRS	interactive voice/web response system
LBT	liver biochemical test
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
MAD	multiple ascending doses
MELD	Model for End-Stage Liver Disease
MIST	metabolites in safety testing
MMP	matrix metalloproteinase
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NOAEL	no observed adverse effect level
NRS	numerical rating scale
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PSC	primary sclerosing cholangitis
PT	prothrombin time
QD	once daily
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOC	System organ class
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
UC	ulcerative colitis
UDCA	ursodeoxycholic acid

Abbreviation	Definition
ULN	upper limit of normal
WOCBP	women of childbearing potential
WONCBP	women of nonchildbearing potential

5 INTRODUCTION

5.1 Investigational Medicinal Product

A3907 is an oral, systemically available, potent inhibitor of the apical sodium bile acid transporter (ASBT). Bile acids are synthesised in the liver from cholesterol and excreted into the small intestine via the gallbladder. The majority of the bile acids secreted from the liver are reabsorbed in the distal part of the ileum via ASBT and then transported into the portal vein where they re-enter the liver, completing the enterohepatic circulation of bile acids. The bile acids that escape intestinal absorption are excreted into the faeces and those that escape hepatic uptake spill into the systemic circulation and are filtered by the kidney; circulating bile acids are almost completely reabsorbed by the proximal renal tubules via ASBT. Furthermore, ASBT is expressed within the bile ducts in cholangiocytes where it is involved in hepatobiliary transport of bile acids to hepatocytes for re-secretion into the bile. Elevated levels of liver and serum bile acids have been implicated in the pathogenesis of cholestatic liver diseases (Jansen, 2018). Lowering bile acid levels and modulating bile acid transport within the bile ducts might subsequently reduce hepatic cell damage in cholestatic liver diseases.

5.2 Background

5.2.1 Primary Sclerosing Cholangitis

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 prevalence of PSC has been estimated to be 1.32 and 2.43/10,000 persons in the United States and European Union, respectively, based on conservative estimates (Mehta et al., 2021; Tabibian et al., 2018). The disease represents an important cause of morbidity and mortality, with many patients ultimately requiring liver transplantation due to end-stage liver disease or other complications (Tabibian et al., 2018). Complications involving the biliary tree are common and include cholangitis as well as ductal strictures and gallstones, both of which may require frequent endoscopic or surgical interventions. Median survival for PSC patients has been estimated previously to be 8 to 12 years from diagnosis in symptomatic patients, depending upon stage of the disease at the time of diagnosis (Lee & Kaplan, 1995; Levy & Lindor, 2006; Worthington & Chapman, 2006). Patients with PSC are also at significantly increased risk of colorectal cancer,

particularly in the up to 90% of patients who also have inflammatory bowel disease (IBD) (Fausa et al., 1991; Loftus et al., 2005; Tabibian et al., 2018; Tung et al., 1996). Cholangiocarcinoma is the most common form of hepatobiliary tract cancer and drastically worsens mortality.

Patients are diagnosed with PSC by the presence of cholestasis when screening at risk patients (e.g. those with IBD) or during general health screening. Symptoms typically develop with progression of the disease, and include fatigue, pruritus, and right upper quadrant pain, potentially accompanied by jaundice in later stages. Diagnosis of PSC is deduced through evaluation of liver biochemistry and symptoms and confirmed by cholangiography using either magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Reports of elevated alkaline phosphatase (ALP are noted in patients with PSC, consistent with cholestasis; however, this is not consistently observed across patients. Alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) may also be elevated. Bilirubin is often normal in early-stage- PSC but increases with progression of the disease. The mean age at diagnosis is 40 years and men are affected twice as often as women.

The only disease-modifying intervention for PSC is liver transplantation. Ursodeoxycholic acid (UDCA) is approved in some countries for treatment with PSC and can improve serum liver test and surrogate markers of prognosis. Symptomatic treatment can relieve itching, acute cholangitis, and fat-soluble vitamin deficiency.

5.2.2 PSC with Clinically Relevant Stricture

Strictures are a common radiographic finding in PSC. Dominant strictures are defined as a biliary stricture observed on ERCP with a diameter of ≤ 1.5 mm in the common bile duct or of ≤ 1 mm in the hepatic duct with further delineation in the definition as a high-grade stricture when there is a > 75% reduction in the common bile duct on magnetic resonance imaging (MRI) (Bowlus et al., 2023). A clinically relevant stricture is a high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis. A clinically relevant stricture is a high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis. Forty (40) to 58% of patients with PSC will develop radiographically apparent strictures (Aljiffry et al., 2011) and

in 15 to 20% of patients with PSC (Hilscher et al., 2018), a localized CRS is the most prominent feature at diagnosis. Individuals with CRS may be considered a different population in PSC and could be stratified as a cohort separate from those who do not have CRS. The presence of an untreated CRS, even in the absence of bile duct malignancy, has been associated with more advanced liver disease histologically, increased liver stiffness assessment via Fibroscan, facilitation of bacterial colonization, increased risk for cholangiocarcinoma, significantly reduced survival, and, if the stricture is accompanied by high-grade dysplasia, earlier liver transplantation should be considered (EASL, 2022).

Patients with CRS's are often excluded from PSC clinical trials, especially if a biliary intervention (stent, dilatation) has occurred within the 3 months prior to the Screening Visit. Clinically relevant strictures are typically managed by endoscopic or surgical interventions such as stenting, or dilatation, or resection. These procedures are not without risk and can include recurrent bleeding, infection, bacterial cholangitis, perforation, or pancreatitis. Balloon dilatations of CRS usually need to be repeated at intervals of 1 to 4 weeks; there is no consensus agreement on dilation protocols; and no results are reported in clinical or biochemical improvement after repeat dilations (EASL, 2022; European Society of Gastrointestinal et al., 2017).

This study will provide important information on the changing landscape of treating patients with PSC and CRS's.

5.2.3 Summary of Clinical and Nonclinical Studies

This is a summary of nonclinical and clinical studies. More detail is provided in the Investigator Brochure.

A series of nonclinical studies were conducted in mice to assess the effect of A3907 on bile acid homeostasis. The studies showed a dose-dependent increase in faecal total bile acid levels confirming ABST inhibition in the ileum. In addition, increases in serum 7α-hydroxy-4-cholesten-3-one (C4) levels and decreases in serum low density lipoprotein cholesterol (LDL-C) were noted, consistent with increased hepatic bile acid biosynthesis.

Due to its systemic availability, A3907 is also anticipated to inhibit ASBT in the kidney in cholestatic conditions, resulting in reduction of bile acid pool through a net loss of bile acids

via urine. Urine primary and secondary bile acid concentrations were significantly, and dose dependently elevated by A3907 treatment in mice.

In addition, A3907 treatment is expected to reduce ASBT mediated bile acid transport within the bile ducts and protect against bile acid induced hepatic cell damage. In in vitro assays, A3907 directly inhibited ASBT and reduced bile acid induced-cholangiocyte proliferation and apoptosis, which are characteristic features of cholestatic liver disease. A3907 treatment has also shown positive effects on biomarkers and liver histology in animal models of cholestatic liver disease. The systemic bioavailability after oral administration of A3907 in mice, rats, and dogs was estimated to be approximately CCI. The time to maximum plasma concentration (T_{max}) was approximately CCI and the apparent terminal elimination half-life ($t_{1/2}$) was approximately CCI. The maximum plasma concentration (C_{max}) increased after increasing oral doses suggesting dose-dependent pharmacokinetics (PK).

Secondary pharmacology and an International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7 core of in vitro and in vivo safety pharmacology studies evaluating A3907 doses up to CCI mg/kg/day showed no adverse effects of concern, and toxicology studies showed that A3907 had a tolerable safety profile. CCI

CCI

A3907 showed no genotoxic potential invitro and administration to pregnant rats and rabbits during organogenesis in preliminary embryo foetal development studies showed no adverse effects on foetal survival, growth, or development.

In a first-in-human (FIH) study (Study A3907-001), A3907 or matching placebo were administered in capsules to healthy subjects as single oral doses of [redacted] to [redacted] mg or CCI oral doses of CCI mg for 7 days. Overall, A3907 was well tolerated when administered as single and multiple ascending doses (SAD/MAD) to the healthy subjects. There were no serious adverse events (SAEs), all treatment-emergent adverse events (TEAEs) were mild in

severity, and no subjects discontinued study drug or withdrew from the study due to TEAEs. The only treatment-related AEs that occurred in ≥ 2 subjects following single or multiple doses of A3907 were diarrhoea, abdominal pain, and headache. Pharmacokinetic analysis revealed that, with this formulation, A3907 was slowly absorbed (T_{max} approximately CCI hours) and dose proportionality was demonstrated at single doses of CCI; the higher single dose of C mg did not result in increased exposure. No accumulation was seen following multiple CCI doses of CCI mg for 7 days, consistent with a half-life of approximately CCI hours. An increase in serum C4 concentrations and a decrease in serum LDL-C concentrations was observed at all A3907 doses; exploratory PK/pharmacodynamics (PD) results suggested a weak correlation between these PD parameters and A3907 PK parameters. While no clear trends were seen between A3907 concentrations and serum total bile acid concentrations, there was a decrease in total urine bile acids excreted at all treatment doses compared to placebo. Together, results of this study suggest that A3907 does inhibit ASBT but the net effect in the intended population is yet to be determined.

5.3 Rationale

A3907 is under development as an oral treatment of cholestatic liver disease, including PSC.

As there is no known medical treatment that slows disease progression, this remains an unmet medical need for patients with PSC. Disease progression is influenced by altered bile acid flow due to biliary complications often observed in patients with PSC, which also contributes to symptoms such as pruritus. Modifying the circulating bile acid pool and reducing the bile acid load may, therefore, have positive effects on PSC disease progression and symptoms.

A3907 is a systemically available, potent, selective inhibitor of the ASBT that has been shown to inhibit both intestinal, renal, and bile duct bile acid transport:

- Pharmacological inhibition of intestinal ASBT by A3907 leads to a net loss of bile acids via faeces.,
- Due to its systemic availability, A3907 is also anticipated to inhibit ASBT in the kidney in cholestatic conditions, resulting in reduction of circulating bile acids through a loss of bile acids via urine.

- Treatment with A3907 is expected to reduce ASBT -mediated bile acid transport within the bile ducts and protect against bile-acid induced hepatic cell damage. This is supported by positive effects demonstrated on biomarkers and liver histology in animal models of cholestatic liver disease and reduction in bile acid induced cholangiocyte proliferation and apoptosis, which are characteristic features of cholestatic liver disease.

5.4 Dose Rationale

A3907 has been extensively evaluated in nonclinical studies and has been shown in vitro and in vivo to effectively inhibit ASBT. The dose selected for this study is based on data collected in nonclinical studies, as well as safety data generated from the FIH study (A3907-001).

In Study A3907-001, A3907 in a capsule formulation was administered to healthy subjects in single doses (SAD) ranging from [redacted] mg tc CCI mg, and multiple doses (MAD) ranging from [redacted] CCI up tc CCI for 7 days. Administration of A3907 was well tolerated after single and 7-day repeated doses, and there were no clinically relevant safety findings at any of the dose levels. In the SAD study, the geometric mean of C_{max} and AUC were CC ng/mL and CCI ng h/mL respectively, and the highest C_{max} and AUC values were CC ng/mL and CCI ng h/mL respectively. In the MAD study, a mean C_{max} of CCI ng/mL and AUC of CCI ng h/mL was observed at the CCI dose at steady state. Pharmacodynamic effects were observed with an increase in C4, a biomarker of bile acid synthesis; a reduction in LDL-C; and a post-prandial increase in serum bile acids at all A3907 dose levels administered for 7 days.

In this 12-week study, A3907 doses of 10 and 30 mg QD (Arms 1 and 2, respectively), and 30 mg BID (Arms 3 and 4) in a tablet formulation will be administered to 6 patients per arm. CCI [redacted] CCI [redacted] These doses are expected to result in exposures predicted to be pharmacodynamically active based on pre-clinical mouse disease models. A3907 has been administered orally for three months to rats and dogs in toxicology studies at doses up to CCI mg/kg/day, respectively, with no adverse findings at any of the dose levels explored. CCI [redacted]

CCI

CCI). In this study, individual PK values may vary due to factors such as gastrointestinal transit time, presence of food, volume of contents within the gastrointestinal tract, and liver impairment. Additionally, A3907 will be administered in a tablet formulation. CCI

CCI

To mitigate risks related to potential variability in PK, patients will first receive a single daily dose of A3907 (10 mg once daily [QD] in Arm 1, 30 mg QD in Arm 2, or 30 mg twice daily [BID] in Arms 3 and 4). After review of each patient's PK data, if the systemic exposures do not exceed the highest systemic exposure previously established in the single dose part of Study A3907-001, CCI the dose will be confirmed, and the patient will begin administration of A3907 QD or BID for 12 weeks. If the exposures exceed the highest systemic exposure previously achieved in healthy subjects in the SAD part of Study A3907-001, individual patients will be terminated early.

5.5 Risk/Benefit Assessment

Risk assessment

A3907 has been administered to 56 healthy subjects in the FIH study (A3907-001). This study demonstrated that A3907 was well tolerated at a dose of up tc CCI in the SAD study and CCI capsule formulation) administered daily for CCI in healthy subjects in the MAD study. The potential risks to study participants associated with A3907 are described in the Guidance to Investigator section of the Investigator's Brochure. The most common A3907-related AEs in the FIH study were diarrhoea, abdominal pain, and headache. Pharmacokinetic analysis revealed that A3907 was slowly absorbed (T_{max} approximately CCI C hours) and dose proportionality was demonstrated at single doses of CCI ; a slightly less than dose proportional- increase was observed with multiple doses of CCI to CCI for 7 days. Repeat doses of A3907 resulted in CCI

in the SAD study, and CCI [redacted] in the MAD study. Nonclinical secondary and safety pharmacology studies, general toxicity studies, and in vitro genotoxicity studies have also been conducted with no adverse effects of concern identified. Nonclinical toxicology studies of A3907 showed no signs of acute toxicity following single repeated oral dosing in rats and dogs up to a dose of CCI mg/kg/day and CC mg/kg/day, respectively, for up to 13 weeks. Elevated ALP and/or ALT values were observed at a dose of CCI mg/kg/day in the 7- and 14-day repeat dose studies in the dog; however, the elevations were fully or almost fully reversed at the end of the recovery phase. Elevations in liver enzymes were not observed in the 13-week dog study or the FIH study.

This is the first time A3907 will be administered to patients with PSC. Potential risks in the patient population are unknown. The potential risks associated with A3907 treatment will be mitigated by routine monitoring as noted in Section 9.3. The study has been designed with a lead-in period to determine the exposure of A3907 in individual patients to ensure that exposure levels observed at the highest dose level in A3907-001 are not exceeded. Additionally, enrollment into Arm 2 will only begin after at least 3 patients in Arm 1 have completed 2 weeks of treatment at the lower dose and an SRC has reviewed safety and PK data (Section 10.2.5). For Arms 3 and 4, enrollment will only begin after at least 3 patients in Arm 2 have completed 2 weeks of treatment at the 30 mg dose QD dose, and an SRC has reviewed safety and PK data (Section 10.2.5). The SRC will also review safety data from this study on an ongoing basis and after the last patient reaches 12 weeks. Thus, exposure of patients in this study is justified by the anticipated benefits that may be afforded to the wider population of patients by continued development of A3907.

Benefit assessment

This study is designed to evaluate the safety, tolerability, PK, and PD of A3907 in patients with PSC. The dose selected is expected to reduce bile acid transport, leading to a decrease in serum bile acids, and positively influence liver enzymes and markers of liver fibrosis. It is not known whether patients participating in this study will benefit from the treatment. Due to the short duration of this study, any benefit observed is not expected to persist beyond the end of the study. However, the increased understanding of the effects of A3907 in this population may potentially result in new treatment options that would ultimately benefit patients with PSC.

5.5.1 Risk/Benefit of Receiving COVID-19 Vaccine during Trial Participation

Nonclinical: Bile acids in general are not expected to perturb immunological responses. No signs of immunological reactions have been seen in clinical studies thus far. Based on the outcome from the standard toxicity studies and the general profile and mechanism of action of A3907, the risk of immunotoxicity has been considered low and dedicated immunotoxicity studies have not been performed.

Clinical: The FIH study did not report any safety signal or trends relative to immunological reactions, which was consistent with the nonclinical data. No trends or safety signals were observed as it relates to haematology including white blood cell count, differential counts, and C-reactive protein. No events of allergic reactions to A3907 or its excipients have been reported.

The risk of an undesirable outcome after receiving the COVID-19 vaccine while treated with A3907 has not been studied and is unknown.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objectives

The primary objective of this study is to evaluate the safety and tolerability of A3907 in patients with PSC with and without a CRS following repeat doses.

6.1.2 Secondary Objectives

The secondary objectives are:

- 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

6.1.3 Exploratory Objectives

The exploratory objectives are:

- 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 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

6.2 Study Endpoints

6.2.1 Primary Endpoints

The primary endpoint is:

- Safety and tolerability as determined by the incidence of TEAEs through Week 12

6.2.2 Secondary Endpoints

The secondary endpoints are:

- 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 (ALT and aspartate aminotransferase [AST]), gamma-glutamyl transferase (GGT), 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)

6.2.3 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
- Change 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 dosing versus the 12 weeks after dosing

Additional Exploratory Endpoints, Arm 4 Only

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

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan

7.1.1 Description

This is an open-label, Phase 2 study to evaluate the safety, tolerability, PK, and PD effects of 3 dose levels of A3907, 10 mg (Arm 1), 30 mg (Arm 2) administered orally QD, or 30 mg BID in Arms 3 and 4 for 12 weeks in patients with PSC with and without a CRS (Figure 1). Eligible patients must have a clinical diagnosis of large-duct- PSC as 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 the Screening Visit and 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 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 the 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 CCI [redacted] CCI [redacted] 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.

Enrollment 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. Enrollment into Arms 3 and 4 will occur

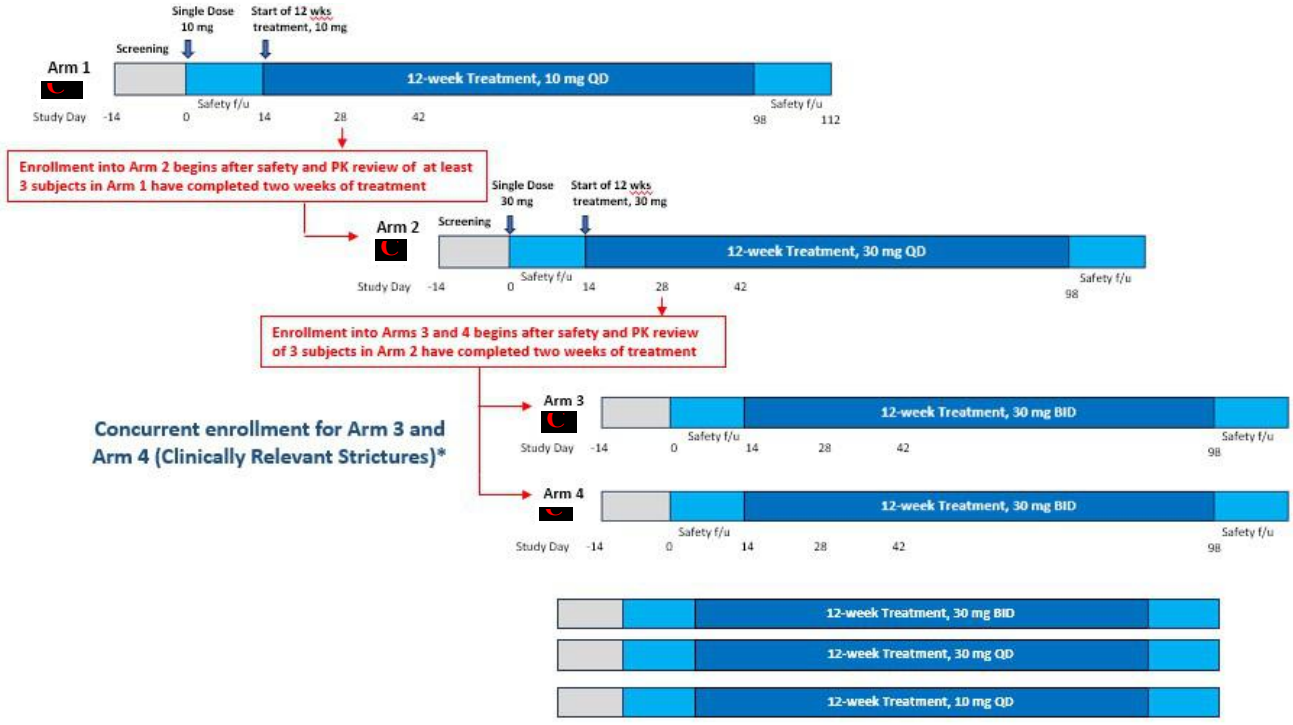
concurrently beginning after at least 3 patients in Arm 2 have completed 2 weeks of treatment and an internal SRC has reviewed safety and PK data.

Study data will also be reviewed by the SRC at regularly scheduled meetings, as described in the SRC charter. The SRC will also convene ad-hoc meetings as necessary. The SRC will also review an optional interim analysis that may be completed when the last patient in any arm has reached 4 weeks of treatment.

There will be a total of 8 scheduled visits during the study (including 1 Screening Visit).

Patients not meeting eligibility criteria may be re-screened once, after consultation with the medical monitor. Laboratory values that are within the inclusion and exclusion criteria are to be repeated to determine if the patient can enter the treatment period. Patients not fulfilling inclusion/exclusion criteria thereafter will not be allowed into the study.

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

Patients will be instructed on the daily use of a Patient Diary. The Patient Diary will include NRSs for evaluation of pruritus (only patients with pruritus at the Screening Visit), fatigue, and sleep disturbance (see Appendix 1), and a Likert scale to assess mood throughout the study. Additionally, patients will be requested to use the Patient Diary to report study drug administration during the Treatment Period. Patient Diaries will be collected at each study visit and the next diary distributed.

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. With the exception of patients that discontinue due to an adverse event, 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.

7.1.2 Schedule of Assessments

The schedule of assessments for the Screening Period through the End-of-Study Visit is presented in Table 1.

Table 1 Schedule of Assessments

Study Activity	Screening Period	Single Dose	Treatment Period					End of Study Visit[a]
			Start of 12-week Treatment Period	2 Weeks	4 Weeks	8 Weeks	12 Weeks/ EOT[b]	
Study Days (window)	**-14 (±2)**	**0**	**14 (±2)**	**28 (±2)**	**42 (±2)**	**70 (±2)**	**98 (±2)**	**112 (±2)**
Visits	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical and surgical history[c]	X	X						
Documentation of endoscopic biliary dilation data (Arm 4 only)	X	X					X	
Vital signs[d]	X	X	X	X	X	X	X	X
Dispense and train on Patient Diary	X	X	X	X	X	X	X	
Study treatment administration:								
A3907 administration[e]		X	X					
Study drug compliance[f]				X	X	X	X	
Pharmacokinetics and Pharmacodynamics[g]:								
Blood sampling for A3907[h]		X	X	X	X	X	X	X
Blood sampling for metabolites (MIST)[i]		X					X	
Blood sampling for serum total and individual bile acids[j]	X	X	X	X	X	X	X	X
Blood sampling for FGF-19[k]		X	X		X		X	
Blood sampling for C4[k]		X	X		X		X	
Blood sampling for biomarkers[l]		X	X		X		X	X
Urine sampling for individual and total bile acids[m]		X	X		X		X	X

Study Activity	Screening Period	Single Dose	Treatment Period					End of Study Visit[a]
			Start of 12-week Treatment Period	2 Weeks	4 Weeks	8 Weeks	12 Weeks/ EOT[b]	
Study Days (window)	**-14 (±2)**	**0**	**14 (±2)**	**28 (±2)**	**42 (±2)**	**70 (±2)**	**98 (±2)**	**112 (±2)**
Visits	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
MELD Score Calculation (Arm 4 only)		X					X	
Safety and Tolerability:								
Adverse event recording	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X
Clinical chemistry[n]	X	X	X	X	X	X	X	X
Hematology[n]	X		X	X	X	X	X	X
Hepatitis B and C	X							
Alpha Fetoprotein	X							
Coagulation[n]	X		X		X		X	
Urinalysis[n]	X	X	X	X	X	X	X	X
Confirmatory FSH test for WONCBP[o]	X							
Serum Pregnancy Test[p]	X							
Urine Pregnancy test for WOCBP[q]		X	X	X	X	X	X	X
12 lead ECG[r]	X	X			X		X	
Fibroscan[s]	X		X		X		X	X
MRCP[t]	X							
Physical examination	X	X			X		X	X
Pruritus NRS lead question[u]	X							
Patient Diary Review[v]	X	X	X	X	X	X	X	X
Faecal calprotectin[w]		X	X	X	X	X	X	X

AFP = (alpha-fetoprotein); C4 = (7α-hydroxy-4-cholesten-3-one); CA 19-9 = carbohydrate antigen 19-9; ECG = electrocardiogram; ERCP = endoscopic retrograde cholangiopancreatography; ELF = enhanced liver fibrosis; EOT = End-of-Treatment; FGF-19 = fibroblast growth factor 19; FSH = follicle stimulating hormone; hsCRP = high-sensitivity C-reactive protein; MIST = metabolites in safety testing; MMP = matrix metalloproteinase; MRCP = magnetic resonance cholangiopancreatography; NRS = numerical rating scale; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] The EOS visit is required 14 (+/-2 days) following Visit 7 or the date of last dose for patients who prematurely discontinue treatment.

[b] An EOT visit must be performed as soon as possible after premature drug discontinuation. If the patient is terminated after Visit 2 due to high exposure, an End-of-Study Visit should be conducted.

[c] Any new medical or surgical history findings after the Screening Period (Visit 1) will be reported as an AE, not as patient medical or surgical history.

[d] To include height (Screening only), weight, temperature, pulse, and systolic and diastolic blood pressure. Vital sign measurements should be taken before A3907 administration.

[e] The last dose of study drug is planned to be administered at Visit 7. The first of the BID doses will be administered at the clinic and patients will be instructed to take the second of the BID doses at home, 12 hours after the first dose was received.

[f] Patients will return all unused study drug at Visit 4, Visit 5, Visit 6, and Visit 7. The study site staff will count all returned drug, assess compliance, and record drug accountability.

[g] Patients will fast for 4 hours prior to all pre-dose blood samples.

[h] Plasma PK samples for Arm 1+2 will be obtained on Day 0 (Visit 2) and Day 98 (Visit 7) pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8 and 10 hours post-dose (± 5 minutes). Plasma PK samples for Arm 3+4 will be obtained on Day 0 (Visit 2) pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 hours post-dose (± 5 minutes). The 12-hour sample collection will be obtained post administration of the first BID dose, but before administration of the second BID dose, and the 24-hour sample collection will be obtained before study drug administration the following morning. On Day 98 (Visit 7), PK samples for Arm 3+4 will be obtained pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 10 hours post-dose (± 5 minutes). The post-dose sample collections will be obtained post administration of the first BID dose. Sampling timepoints at Day 98 (Visit 7) may be adjusted based on observed data from Day 0 (Visit 2) without changing the total number of blood samples. For Visits 3 to 6 (inclusive), PK will be collected once pre-dose, and once for Visit 8. In the case of hepatic adverse events and/or hepatic decompensation, a PK sample should be collected as close to the onset of the event as possible. In the case of hepatic adverse events and/or hepatic decompensation, a PK sample should be collected as close to the onset of the event as possible.

[i] Metabolites (MIST) samples will be obtained on Day 0 (Visit 2) and Day 98 (Visit 7) pre-dose, 2, 4, 8 and 12 hours post dose (± 5 minutes). Sampling timepoints may be adjusted based on observed data from Day 0 (Visit 2) without changing the total number of blood samples.

[j] Serum bile acid levels will be obtained once per applicable visit, pre-dose. Serum bile acid levels will be obtained once on Visit 8.

[k] Serum samples for C4 and FGF-19 will be obtained once per applicable visit, pre-dose.

[l] Biomarkers include autotaxin, ProC3, hsCRP, MMP7, MMP9, ELF score, AFP and CA 19-9. Serum samples will be obtained once per applicable visit—pre–dose. Serum samples will be obtained once on Visit 8.

[m] Urine will be collected by the patient for the 24-hour period prior to study visit.

[n] The safety laboratory parameters to be assessed are presented in Table 2.

[o] Confirmatory FSH for women of WONCBP upon Screening.

[p] Serum pregnancy test for all women upon Screening.

[q] Urine pregnancy tests for WOCBP should 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 hCG blood pregnancy test will be performed.

[r] The 12 lead ECG should be performed with the patient in supine rest for at least 5 minutes prior to blood sample collection.

[s] Performed where available, as per institution standard practice.

[t] MRCP is only applicable for patients without MRCP or ERCP results available <6 months prior to Screening.

[u] Site staff will assess pruritus at the Screening Visit by having patients respond to a dichotomous yes/no question asking if they have "experienced pruritus in the past 7 days."

[v] Patient Diary will include pruritus NRS and/or fatigue NRS, sleep disturbance NRS, mood Likert scale, and study drug compliance and 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.

[w] Stool samples will be collected at home for patients with inflammatory bowel disease. Sampling kits will be provided to patients for at-home collection.

7.1.3 Study Procedures and Assessments

For all visits occurring after informed consent is obtained, patients will fast for 4 hours prior to study visit.

7.1.3.1 Screening Period

Day -14/Clinic Visit 1

Screening procedures and assessments are as follows:

- Obtain written informed consent (if not fasting at time of consent, patient will return to complete Visit 1 assessments after having fasted for 4 hours)
- Assess inclusion/exclusion criteria (Sections 7.2.2 and 7.2.3)
- Record demographics (Section 9.2)
- Document prior medications
- Medical and surgical history
- Physical examination (Section 9.3.2) and vital signs (Section 9.3.3)
- 12-lead electrocardiogram (ECG) (Section 9.3.7)
- Blood sampling for serum total and individual bile acids (Section 9.5.1)
- Screening laboratory assessments (hematology, clinical chemistry, urinalysis, and coagulation [Section 9.3.5]; Hepatitis B and C, alpha-fetoprotein (AFP))
- Confirmatory follicle-stimulating hormone (FSH) for post-menopausal females without documentation of being surgically sterile (Section 9.3.18)
- Serum pregnancy test for all women
- AE monitoring (Section 9.3.4)
- Fibroscan (Section 9.3.8)
- MRCP, unless conducted within the 6 months prior to the Screening Period (Section 9.3.9). A confirmatory MRCP is also required if a historical MRCP or ECRP is not completed within 6 months of the Screening Period.
- Pruritus NRS lead question (Section 9.3.12)
- Patient Diary distribution, training, and compliance requirements; patients begin daily recording of pruritus, fatigue, and sleep disturbance NRS and mood Likert Scale (Section 9.3.12 to Section 9.3.15)
- Documentation of endoscopic biliary dilation data (Arm 4 only)

7.1.3.2 Treatment Period

Study Day 0/Visit 2

The following procedures and assessments will be conducted:

- Assess inclusion/exclusion criteria (Sections 7.2.2 and 7.2.3)
- Medical and surgical history. Any new medical or surgical history findings after the Screening Period (Visit 1) will be reported as an AE, not as patient medical or surgical history.
- Documentation of endoscopic biliary dilation data (Arm 4 only)
- Physical examination (Section 9.3.2) and vital signs (Section 9.3.3)
- Study drug administration
- Review of Patient Diary for compliance (e.g. mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS) and distribution of next diary.
- 12-lead ECG (Section 9.3.7)
- Blood sampling for A3907, metabolites in safety testing (MIST), FGF-19, C4, biomarkers, and serum total and individual bile acids (Section 9.5.1)
- Collect 24-hour urine sample for bile acid assessment (Section 9.5.1)
- Urine pregnancy test for women of childbearing potential (WOCBP)
- MELD Score (Arm 4 only)
- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)
- Clinical chemistry, urinalysis (Section 9.3.5)
- 12-lead ECG (Section 9.3.7)
- Stool sample for faecal calprotectin (Section 9.3.11)

Study Day 14/Visit 3

The following procedures and assessments will be conducted:

- Vital signs (Section 9.3.3)
- Study drug administration
- Review of Patient Diary for compliance (e.g., mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS) and distribution of next diary.
- Blood sampling for A3907, FGF-19, C4, biomarkers, and serum total and individual bile acids (Section 9.5.1)
- Collect 24-hour urine sample for bile acid assessment (Section 9.5.1)
- Urine pregnancy test for WOCBP

- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)
- Clinical chemistry, hematology, coagulation, and urinalysis (Section 9.3.5)
- Fibroscan (Section 9.3.8)
- Stool sample for faecal calprotectin (Section 9.3.11)

Study Day 28/Visit 4

The following procedures and assessments will be conducted:

- Vital signs (Section 9.3.3)
- Study drug administration
- Study drug compliance (Section 8.4)
- Review of Patient Diary for compliance (e.g. mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS) and distribution of next diary.
- Blood sampling for A3907, and serum total and individual bile acids (Section 9.5.1)
- Urine pregnancy test for WOCBP
- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)
- Clinical chemistry, hematology, and urinalysis (Section 9.3.5)
- Stool sample for faecal calprotectin (Section 9.3.11)

Study Day 42/Visit 5

The following procedures and assessments will be conducted:

- Physical examination (Section 9.3.2) and vital signs (Section 9.3.3)
- Study drug administration
- Study drug compliance (Section 8.4)
- Review of Patient Diary for compliance (e.g. mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS) and distribution of next diary.
- Blood sampling for A3907, FGF-19, C4, biomarkers, and serum total and individual bile acids (Section 9.5.1)
- Collect 24-hour urine sample for bile acid assessment (Section 9.5.1)
- Urine pregnancy test for WOCBP
- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)
- Clinical chemistry, hematology, coagulation, and urinalysis (Section 9.3.5)

- 12-lead ECG (Section 9.3.7)
- Fibroscan (Section 9.3.8)
- Stool sample for faecal calprotectin (Section 9.3.11)

Study Day 70/Visit 6

The following procedures and assessments will be conducted:

- Vital signs (Section 9.3.3)
- Study drug administration
- Study drug compliance (Section 8.4)
- Review of Patient Diary for compliance (e.g. mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS) and distribution of next diary.
- Blood sampling for A3907 and serum total and individual bile acids (Section 9.5.1)
- Urine pregnancy test for WOCBP
- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)
- Clinical chemistry, hematology, and urinalysis (Section 9.3.5)
- Stool sample for faecal calprotectin (Section 9.3.11)

7.1.3.3 End-of-Treatment/Early Termination

Study Day 98/Visit 7

The following procedures and assessments will be conducted:

- Physical examination (Section 9.3.2) and vital signs (Section 9.3.3)
- Study drug administration
- Study drug compliance (Section 8.4)
- Review of Patient Diary for compliance (e.g. mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS) and distribution of next diary.
- Documentation of endoscopic biliary dilation data (Arm 4 only)
- Blood sampling for A3907, MIST, FGF-19, C4, biomarkers, and serum total and individual bile acids (Section 9.5.1)
- Collect 24-hour urine sample for bile acid assessment (Section 9.5.1)
- Urine pregnancy test for WOCBP
- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)

- Clinical chemistry, hematology, urinalysis, and coagulation (Section 9.3.5)
- 12-lead ECG (Section 9.3.7)
- Fibroscan (Section 9.3.8)

7.1.3.4 Stool sample for faecal calprotectin (Section 9.3.11)End-of-Study/Follow-up Visit

Study Day 112/Visit 8

Patients will return to the study site 14 days after Visit 7 or the last dose of study drug (for those patients who prematurely discontinue) for the following assessments:

- Review of Patient Diary for compliance (e.g. mood Likert Scale, and pruritus [as applicable], fatigue, and sleep disturbance NRS
- Physical examination (Section 9.3.2) and vital signs (Section 9.3.3)
- Blood sampling for A3907, biomarkers, and serum total and individual bile acids (Section 9.5.1)
- Collect 24-hour urine sample for bile acid assessment (Section 9.5.1)
- Urine pregnancy test for WOCBP
- AE monitoring (Section 9.3.4)
- Document concomitant medications (Section 9.3.1)
- Clinical chemistry, hematology, and urinalysis (Section 9.3.5)
- Fibroscan (Section 9.3.8)
- Stool sample for faecal calprotectin (Section 9.3.11)

7.2 Study Population

7.2.1 Number of Patients

Approximately 24 patients are expected to be treated in this study. Six patients are planned to enroll in each of the 4 treatment arms of the study.

7.2.2 Inclusion Criteria

Patients meeting all of the following criteria will be considered eligible for enrollment in the study:

Diagnosis and Criteria for Inclusion:

1. Adults between 18 and 75 years of age (inclusive).

2. Have a clinical diagnosis of large-duct PSC with evidence of more than 6 months duration with either a consistent MRCP or ERCP showing sclerosing cholangitis and historical evidence of elevated ALP.
3. Willing to sign informed consent.
4. Women of childbearing potential (WOCBP) and males with female partners of childbearing potential must agree to use contraception as detailed in Section 9.3.18. Women of nonchildbearing potential (WONCBP) must meet the definition in Section 9.3.18 and have a confirmatory FSH level ≥ 40 mIU/mL.
5. ALP value > 1.5 × ULN but ≤ 10 × ULN at Visit 1 (Screening). Before starting 12 weeks treatment variability of < 30% between ALP values at Visit 1 and Visit 2 must be confirmed. If variability is >30 % a third ALP value may be obtained. If the third ALP value meets >1.5 × ULN but ≤ 10 × ULN the patient can start the 12-week treatment period.
6. Arms 1-3 Only: Total bilirubin < 1.5 × ULN (unless due to Gilberts Syndrome or hemolysis) and normal direct bilirubin.
7. AST and ALT ≤ 5 × ULN
8. Serum bile acid level > ULN
9. Arms 1 - 3 Only: An MRCP or equivalent imaging modality performed within 6 months before the Screening Period that is consistent with PSC without a CRS,
10. Arm 4 Only: An MRCP or equivalent imaging modality performed within 6 months before the Screening Period that is consistent with PSC with a CRS, or clinically relevant bile duct obstruction (see Inclusion # 12 for additional information).
11. Use of UDCA with a total daily dose ≤ 23 mg/kg/day, or bile acid-binding resins are permitted, with a minimum of 3 months of stable treatment prior to the Screening Period, and expected to remain on a stable dose through the 12-week treatment period; or a minimum of 3 months off UDCA prior to the Screening Period if UDCA was recently discontinued.
12. If a patient has (IBD with a minimum disease duration of 4 weeks, this diagnosis should be documented. Inflammatory bowel disease should be in clinical remission or mildly active according to Crohn's Disease Activity Index (CDAI), partial Mayo score for Crohn's Disease (CD and ulcerative colitis (UC), respectively (i.e. patients with CDAI score < 220 and Mayo score < 5, respectively). Patients with IBD should have had a colonoscopy performed within one year prior to the Screening Period with results showing no evidence of dysplasia or cancer.
13. Clinically stable for at least 3 months prior to the Screening Period

14. Arm 4 Only: One stable clinically relevant biliary stricture of at least 4 weeks duration on contrast-enhanced MRI/MRCP with > 75% reduction of duct diameter in the common bile duct or hepatic duct without suspicion of cholangiocarcinoma (further established by imaging and stable CA 19-9 below ULN repeated twice over 1 month), or cholelithiasis. Subjects may have signs or symptoms of worsening obstructive cholestasis (increasing jaundice, nausea, anorexia, steatorrhea and worsening or new onset pruritus), deterioration of liver function (i.e. decreasing platelet count, increasing international normalized ratio [INR]) and/could be listed for liver transplantation due to their clinically relevant biliary stricture.
15. Arm 4 Only: MELD Score < 35

7.2.3 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

Medical History

1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis).
2. Arm 1-3 Only: Biliary intervention within 3 months prior to study enrollment or planned.
3. Arm 4 Only: Planned Biliary intervention between the Screening Period and baseline.
4. Presence of alternative causes of chronic liver disease, including alcohol-associated liver disease, nonalcoholic steatohepatitis, primary biliary cholangitis, autoimmune hepatitis, or active hepatitis B or C.
5. IBD with uncontrolled moderate to severe activity and/or on treatment with any immunosuppressive, immunomodulator, or biologic agent for treatment of IBD (i.e. azathioprine, 6 mercaptopurine, tacrolimus, methotrexate, infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, ozanimod). Treatment with corticosteroids (including budesonide, budesonide MMX and beclomethasone) in the previous 4 weeks.
6. History of human immunodeficiency virus infection or any other known relevant infection (e.g. tuberculosis).
7. History of ileectomy, colostomy or colectomy.

8. History of malignancy, including hepatocellular carcinoma and cholangiocarcinoma within the past 10 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
9. Alpha-fetoprotein (AFP) > 20 ng/mL (at the Screening Visit) with 4-phase liver CT or MRI suggesting presence of liver cancer.
10. History of transplants, including liver transplantation, or currently on active transplantation list (Arms 1-3). Arm 4 may be on an active liver transplantation list.
11. Current or a history of hepatic decompensation events including, but not limited to ascites, encephalopathy, or history of esophageal variceal bleeding.
12. Known or suspected overlapping clinical and histologic diagnosis of autoimmune hepatitis.
13. Small duct PSC (evidence of PSC on historical liver histology, with normal bile ducts on cholangiography) without large duct PSC.
14. Liver cirrhosis as assessed by any of the following:
    a. historical liver histology.
    b. liver stiffness measurement, assessed by FibroScan (FibroScan value > 14.4 kPa), in addition to clinical assessment and biochemical markers at the discretion of the investigator.
    c. signs and symptoms of hepatic decompensation (including, but not limited to, jaundice, ascites, variceal haemorrhage, and/or hepatic encephalopathy).
15. History of bacterial cholangitis within 60 days prior to the Screening Period, or if the patient is on antibiotics for prophylaxis of recurrent cholangitis.
16. Females who are pregnant, lactating, or breast feeding as detailed in Section 9.3.18.
17. History of alcohol or substance abuse in the previous 2 years. Patients must agree to refrain from illicit drug (including marijuana) and alcohol use during the study.
18. Hypersensitivity to investigational medicinal product (A3907) and its excipients.
19. Presence of any contraindication for undergoing MRCP (e.g. pacemaker).
20. Any other condition or abnormality which, in the opinion of the investigator (or designee), may compromise the safety of the patient or interfere with the patient participating in, or completing the study.

Treatment Exclusions:

21. Administration of medications that slow gastrointestinal motility (Section 8.6.2).
22. Treatment with rifampicin.

23. Exposure to oral drugs that are strong inhibitors or inducers of CYP3A4 enzymes (e.g. grapefruit juice, ritonavir, itraconazole, ketoconazole, troleandomycin, rifampin, St John's wort, etc.) within 14 days prior to the Screening Period, or 5 half-lives of the drug, whichever is longer (Section 8.6.2).
24. Exposure to oral drugs that are substrates of CYP3A4 enzymes (e.g. codeine, ciclosporin [cyclosporin], diazepam, etc.) during the study (Section 8.6.2).
25. Treatment with vitamin D or fibrates, unless patient is on a stable dose ≥ 6 months prior to baseline.
26. Exposure to an investigational drug, biologic agent, or medical device within 30 days prior to the Screening Period, or 5 half-lives of the study agent, whichever is longer.

Laboratory Exclusions:

27. Platelet count < 150 000/mm^3.
28. Albumin level < 3.0 g/dL.
29. INR > 1.3 (the patient may be treated with vitamin K intravenously, and if INR is ≤ 1.3 at resampling, the patient may be enrolled).
30. Medical conditions that may cause non-hepatic increases in ALP (e.g. Paget's disease). A GGT or ALP isoenzymes should be obtained for confirmation of biliary origin;
31. Glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2

7.2.4 Withdrawal of Patients

7.2.4.1 Individual Study Drug Interruption and/or Discontinuation

Study drug administration will be discontinued for patients with C_{max} or AUC that exceed the safety margins observed in the FIH study (Section 5.4),)or because of circumstances leading to study withdrawal as detailed in Section 7.2.4.2.

A patient will discontinue dosing but may remain in the study for safety monitoring if any of the following criteria are met:

- A patient's desire to discontinue study drug for any reason.
- Any AE considered related to A3907 that in the opinion of the investigator (or designee) and sponsor's medical monitor poses a risk to the patient's safety or well-being and warrants study drug discontinuation (Section 9.3.6).
- Liver transplantation.
- Pregnancy

- A patient's exposures exceed the arm's highest systemic exposures previously achieved in healthy subject [redacted]

The reason and date the patient is discontinued from the treatment will be documented in the electronic case report form (eCRF). The patient will undergo End-of-Treatment and End-of-Study procedures as defined in Table 1.

7.2.4.2 Withdrawal from Study

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons.

Any withdrawal, and reasons for withdrawal, must be fully documented in the eCRF and source documents and the patient followed by the investigator/investigative staff. Withdrawn patients may be replaced, as needed, to ensure 6 patients are enrolled into the 12-week Treatment Period of each treatment arm.

Patients will be withdrawn in the following circumstances:

- A patient's desire for withdrawal for any reason.
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent).
- An AE which, in the opinion of the investigator (or designee), necessitates withdrawal.
- Death.
- A patient's substantial non-compliance (Patient Diary and study drug compliance) or protocol violation.
- An investigator's (or designee's) opinion that continuing the patient in the study is not appropriate. The investigator (or designee) may withdraw a patient at any time if it is considered to be in the patient's best interest.
- Liver transplantation.
- Pregnancy

The reason and the date the patient is withdrawn from the study will be documented in the eCRF and source documents. If a patient is withdrawn from the study, the investigator/investigative staff will attempt to complete all End-of-Study (Visit 8) procedures within 14 days following premature withdrawal (i.e. 14 days following the final dose of the study drug).

7.2.4.3 Stopping Rules

The study will be halted if any of the following criteria are met:

- ≥ 2 patients experience a severe, nonserious AE that is considered to be related to study drug.
- ≥ 1 patient experiences a serious AE that is considered to be related to study drug.

If, following a SRC review, the sponsor deems it appropriate to restart the study, this can be done following approval of a substantial protocol amendment.

7.2.5 Study Termination by Sponsor

This study may be terminated at any time by Albireo, if significant safety concerns develop or, in the sponsor's judgment, there are no further benefits to be achieved from continuation of the study. In this event, Albireo/designee will inform the study investigators (or designees), institutions, and all regulatory authorities.

Albireo may temporarily or permanently discontinue the study at an investigative site at any time for safety, ethical, compliance, or other reasons. If this is necessary, Albireo will endeavor to provide advance notification to the site. If a site or the study is suspended or discontinued, the investigator/investigative staff will be responsible for promptly informing the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) that this has happened. If required by local regulations, Albireo /designee will be responsible for informing the IEC/IRB and the Regulatory Authority of study or site discontinuation. In such an event, all study data and unused study drug must be returned to Albireo.

Events that could potentially trigger study discontinuation will undergo an expedited review by Albireo's internal Safety Review Team, which will reach an agreement prior to dosing new patients.

8 STUDY TREATMENT

8.1 Study Drug Supply and Storage

A3907 will be supplied in 10 mg tablets for oral administration. Tablets will be packaged and labelled in child-resistant containers with polypropylene caps.

Bottles of A3907 should be stored and dispensed in their original containers. All study drug must be stored according to the package label in a secure, limited-access location and may be dispensed only by the investigator (or designee) or by a member of the staff specifically authorised by the investigator (or designee). A3907 should be stored in a dry, clean, and well-ventilated area at 15°C to 25°C. Any deviations from the recommended storage conditions should be immediately reported to the sponsor and the study drug should not be used until approval by the sponsor.

Additional information on the study drug can be found in the provided study drug manual.

8.2 Study Drug Dose and Administration

Treatment with A3907 will be administered as a QD dose (single10 mg tablet or three 10 mg tablets [30 mg]) or as a BID dose of three 10 mg tablets [30 mg] twelve hours apart on Day 0, followed by a 2-week dose confirmation period, before being administered at the same dose once daily for 12 weeks. Before each patient can begin the 12-week Treatment Period, individual PK evaluations will be conducted to ensure study drug exposure does not exceed that observed in the FIH study. If the exposures exceed the highest systemic exposure as described in Section 5.4, the individual patient will be terminated early.

The dose for Arm 2 may be adjusted, after discussion at the SRC, based on review of PK data from patients in Arm 1, but it will not exceed 30 mg QD. The doses for Arms 3 and 4 may be adjusted, after discussion with the SRC, based on review of the PK data from patients in Arm 1 and 2, but will not exceed 30 mg BID.

Study drug will be dispensed to the patient at defined intervals from Visit 3 through Visit 7 (Table 1), 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.

Patients will be instructed to take the dose with food at approximately the same time each day in the morning. Patients should not crush or chew the tablet(s). Tablets should be

swallowed whole and should not be ingested if they are broken, cracked, or otherwise not intact. When swallowing the tablet intact, the patient should administer the dose with a glass of water. Dosing should not be repeated if a patient vomits after ingesting the daily dose. A QD dose missed by more than 12 hours should be skipped and the next prescribed dose should be taken at the usual time. If either of the BID doses are missed by > 6 hours, the dose should be skipped and the next prescribed dose should be taken at the usual time. If the patient is off A3907 for >5 half-lives of the study drug, the patient will be discontinued from the study.

On clinic visit days when laboratory assessments are conducted, study drug should be taken at the clinic after samples are collected. Patients will be required to fast for 4 hours prior to these study visits and breakfast will be provided at the time the study drug is administered. The first of the BID doses will be administered at the clinic and patients will be instructed to take the second of the BID doses at home, 12 hours after the first dose was received.

8.3 Study Drug Packaging, Labelling, and Blinding

8.3.1 Packaging and Labelling

Study drug will be labelled appropriately as investigational product for this study. Packaging and labelling will be prepared to meet all local regulatory requirements.

8.3.2 Blinding and Randomization of Study Drug

Blinding is not applicable as this is an open-label study. All patients will take A3907 administered orally once daily at approximately the same time each day as described in Section 8.2. Patients will be assigned to treatment arms via an interactive voice/web response system (IXRS).

Patient Identification

After written informed consent is obtained from an eligible patient, an 8-digital patient identification number will be assigned. The first 2 digits will denote the country, followed by a 3-digit site number and a 3-digit patient sequence number. This number will be captured by the IXRS and integrated into the eCRF in Protocol A3907-002.

8.3.3 Procedure for Breaking the Blind

Not applicable as this is an open-label study.

8.4 Patient Compliance

Study drug compliance will be monitored through Patient Diary entries. Any noncompliance will be documented in the source documents. Additionally, patients will return all unused study drug at Visit 4, Visit 5, Visit 6, and Visit 7. The study site staff will count all returned drug, assess compliance, and record drug accountability.

8.5 Study Drug Accountability

Accountability for the study drug at the study site is the responsibility of the investigator (or designee). The investigator (or designee) will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator (or designee) may choose to assign drug accountability responsibilities to an appropriate individual.

The investigator (or designee) will maintain accurate study drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and return to the sponsor or its designee (or disposal of the drug, if approved by the sponsor). These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from the sponsor. Accountability records will include dates, quantities, batch numbers, expiration dates (if applicable), and patient numbers. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

Study drug must not be used for any purpose other than the present study. Study drug which has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

Patients will receive instructions for home administration of study drug along with a Patient Diary to confirm study drug administration.

All unused and used study drug will be retained at the site until they are inventoried by the study monitor. All used, unused, or expired study drug will be returned to the sponsor or its designee or if authorised, disposed of at the study site according to the site's Standard Operating Procedures and must be documented. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

8.6 Concomitant Therapy and Prohibited Medications

All medications administered from screening to 14 days after the last dose of study drug are to be recorded on the eCRF. All medications, including vitamin supplements, over -the -counter medications, and herbal preparations, as well as non-drug therapies, taken throughout the study must be documented in the patient's source documents and eCRF.

All medications taken by a patient within 14 days or 5 times the half-life of the drug, whichever is longer, prior to the first intake of study drug are regarded as prior medication. All medications taken by a patient on or after the first day of study drug intake, and which continue to be taken during the study, are regarded as concomitant medication.

Patients will be instructed not to take any additional medications during the study without prior consultation with the treating physician. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

8.6.1 Permitted Medications

The following concomitant medications are permitted:

- In patients with IBD, in the event of an IBD flare, up to 25 mg of prednisone per day or 9 mg of budesonide/budesonide MMX or 10 mg of beclomethasone may be taken without jeopardizing their participation in the study. Mesalamine or beclomethasone enemas are also admitted medications. If a higher dose of prednisone or a biological agent is needed or the patient needs to be hospitalised for controlling disease activity, then the patient's participation in the study is to be terminated.
- If a patient is taking cholestyramine at the Screening Visit, they should remain on a stable dose during the study, and it should be taken 4 hours after administration of A3907 study drug.
- UDCA is permitted with a total daily dose ≤ 23 mg/kg/day, a minimum of 3 months of stable treatment prior to the Screening Period, and expected to remain on a stable dose through the 12-week treatment period. However, UDCA should not be taken within 4 hours of A3907.
- Vitamin D or fibrates are permitted. Patients must be on a stable dose for at least 6 months prior to starting treatment with A3907.
- Approved vaccines are permitted during the trial.

8.6.2 Excluded Medications and Substances

The following medications are prohibited:

- Medications that slow GI motility (e.g. sucralfate, loperamide, codeine)
- Statins
- Immunosuppressive medication for controlling IBD (e.g. azathioprine, 6 mercaptopurine, tacrolimus, methotrexate, infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, tofacitinib, ozanimod)

Patients will be instructed not to take any of the following medication for 14 days or 5 times the half-life of the drug, whichever is longer, prior to receiving the first dose of the study drug:

- Oral drugs that are strong inhibitors or inducers of CYP3A4 enzymes (e.g. grapefruit juice, ritonavir, itraconazole, ketoconazole, troleandomycin, rifampin, St John's wort, etc.)

Patients will be instructed not to take any of the following medication during the study:

- Oral drugs that are a substrate of CYP3A4 enzymes (e.g. codeine, ciclosporin [cyclosporin], diazepam, etc.)
- Oral drugs that are a substrate of P-gp or breast cancer resistance protein transporters
- Drugs that are a substrate of OATP1B1

9 STUDY ASSESSMENTS

9.1 Informed Consent

A complete description of the study is to be presented to each potential patient and a signed and dated informed consent is to be obtained before any study-specific procedures are performed.

9.2 Demographic Data and Medical History

Demographic information per country regulations, along with medical and surgical history, will be obtained and recorded in the eCRF at Visit 1.

Demographic data collected will include year of birth, age, gender, fertility status for females, and geographic origin. Geographical origin information will be collected in order to evaluate if the outcome is consistent across different sub-groups.

A complete medical and surgical history, including the date of diagnosis of PSC and prior investigational medications for PSC, will be obtained during the Screening Period. The medical history is to include all relevant prior medical history as well as all current medical conditions.

9.3 Safety Assessments

The timing and frequency of safety assessments are described in Section 7.1.2 and Section 7.1.3.

The primary safety analysis for this study will include the incidence of TEAEs, TEAEs leading to discontinuation, and TEAEs categorised by causality, severity, and seriousness assessments.

Trends in safety will also be evaluated for the following assessments:

- Concomitant medications
- Physical examinations
- Vital signs
- Laboratory test results (including clinical chemistry, hematology, urinalysis, and coagulation)

9.3.1 Concomitant Medications

Concomitant medications will be documented in the eCRF for each patient at each scheduled visit. All medications or non-drug therapies administered within 14 days before

the first day of study drug administration should be reported as prior medication in the eCRF. Subsequently, at each study visit, patients will be asked whether they have taken any medication other than the study medication (from the Screening Period through the end of the study). All medications, including vitamin supplements, over-the-counter medications, and oral herbal preparations, as well as non-drug therapies, taken on or after the first day of study drug dose through 14 days after the last dose of study drug must be documented.

Permitted and excluded medications are found in Section 8.6.

9.3.2 Physical Examination

A physician or suitably trained qualified assistant will perform a complete physical examination at times presented in Table 1.

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. Height and weight will also be documented; height will be measured at the Screening Visit only.

9.3.3 Vital Signs

Vital sign measurements, including systolic and diastolic blood pressure, pulse rate, and temperature will be obtained at times presented in Table 1.

Assessments should be conducted while the patient is seated. Vital sign measurements should be taken before A3907 administration.

9.3.4 Adverse Events

9.3.4.1 Safety Reporting Period

Each patient must be carefully monitored for the development of AEs during the safety reporting period.

The safety reporting period for AEs is from signing of the ICF through the last planned study visit or 14 calendar days after the last dose of the study drug, whichever occurs later.

An SAE that occurs following the safety reporting period and which is assessed by the investigator (or designee) as related to study medication should also be reported.

9.3.4.2 Definitions and Investigator Assessments

An AE is defined as any untoward medical occurrence in an enrolled patient regardless of causal relationship with 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 any AE or worsening of an existing disease that occurs after the first dose of study drug and within the 14-day follow-up.

9.3.4.3 Clinical Significance

The investigator (or designee) will review all patient-reported events, laboratory and other test results and use clinical judgment to identify events that are clinically significant. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of a new condition. Patient reported events and protocol mandated laboratory values, vital signs, and physical examination findings can be considered clinically significant (i.e. an AE) if there is a deterioration compared to baseline. Examples of clinically significant worsening from baseline could include, but is not limited to, events causing withdrawal from the study and events requiring medical intervention outside of the study causing apparent clinical manifestations or judged relevant by the investigator (or designee).

9.3.4.4 Serious Adverse Events

Each AE must be classified by the investigator (or designee) as either serious or nonserious. This assessment is made independently of severity assessment. Any AE that meets any 1 of the following criteria is considered an SAE:

- The outcome of the AE is **death.**
- The AE is **life-threatening**, meaning that the patient is, in the opinion of the investigator (or designee), at immediate risk of death from the reaction as it occurred. This does not include an AE that, if more severe, might have caused death.
- The AE results in persistent or significant **disability/incapacity**. Disability means a substantial disruption of a person's ability to conduct normal life functions.
- The AE requires or prolongs **hospitalisation.** In-patient hospitalisation is defined of any stay in the hospital of more than 24 hours, or any admission to a hospital ward or unit as an inpatient.

- Hospitalisations for procedures that were planned prior to study participation are not considered SAEs.
- Hospital admissions for routine diagnostic testing not associated with an AE (e.g. admission due to travel distance) are not considered SAEs.

- The AE results in a **congenital anomaly/birth defect.**
- **The AE is an important medical event**. The investigator (or designee) should apply medical and scientific judgment to assess whether an AE should be classified as serious due to medical significance, even if no other seriousness criteria is met. As a general guideline, medically important events may significantly jeopardise the patient, represent a significant hazard, or require medical/surgical intervention to prevent one of the outcomes listed above. Examples of potential SAEs based on this criterion include, but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions, even if they do not result in inpatient hospitalisation, or the development of drug dependency and drug abuse.

Seriousness assessment is made independently of severity assessment (Section 9.3.4.5). For example, a severe rash may not meet serious criteria as defined above and, therefore, would be considered a severe, non-serious AE.

9.3.4.5 Severity Assessment

Severity assessments are based on the intensity of the event in relation to expectation. The Investigator will assess the intensity of AEs based on the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 grading system as follows[1]:

- Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

[1] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Severity is a measure of intensity whereas seriousness is defined by the criteria outlined in Section 9.3.4.4. An AE of severe intensity need not be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not meet serious criteria, and would, therefore, be assessed as a severe AE but not an SAE.

9.3.4.6 Causality Assessment

The investigator (or designee) will determine the causality of all AEs to the study drug using medical judgment and considering all relevant factors including, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study drug, and de-challenge or re-challenge information. The causality assessment of the AE/SAE is to be made as described below.

Related to study drug (possibly, probably, or definitely related)

Based on medical judgment, there is at least a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.
- The event disappears or decreases on cessation or reduction in dose of the study drug (positive de-challenge). It should be noted that, in some situations, an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness.
- The event reappears or worsens when the study drug is re-administered (positive re-challenge).

Unrelated to study drug (unlikely or unrelated)

Based on medical judgment there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug.

- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors, or other modes of therapy administered to the patient.
- The event does not follow a known pattern of response to study drug.
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered.

Default assessments of the related category without supportive evidence for a causal relationship to study drug is generally uninformative and does not contribute meaningfully to the development of the safety profile of the drug or to patient safety.

9.3.4.7 Recording of Adverse Events

Monitoring of AEs will be conducted throughout the study after patients sign the ICF. Adverse events will be collected for all patients, including screen failures, and recorded in the eCRF for all enrolled patients. It is the investigator's (or designee's) responsibility to assess the severity, seriousness, and causality to study drug for each AE and record it in the eCRF. All AEs and SAEs, regardless of attribution, should be reported until 14 days after the last administration of study treatment or until study discontinuation/termination, whichever occurs later. Patients will be assessed at the End of Study Visit to determine if any new AEs have occurred. After this period, investigators (or designees) should report only SAEs that are considered related to study drug.

Any AEs or SAEs that are unresolved at the patient's last AE assessment in the study are to be followed up by the investigator (or designee) until resolution or stabilization, up to database lock, and recorded in the eCRF. Albireo AB retains the right to request additional information for any patient with ongoing AEs or SAEs at the end of the study.

If there is a clinically significant deterioration of a laboratory value/vital sign or other routine study assessment that is associated with a diagnosis, the clinical diagnosis will be reported as an AE and the associated signs and symptoms will be considered additional information unless the sign or symptom is more severe than expected given the diagnosis. For example, if an investigator (or designee) diagnoses a study patient with hepatitis during the study period, hepatitis would be considered the AE and the concomitant signs and symptoms of abdominal pain, vomiting, and elevated ALT and AST would not be reported separately unless, in the opinion of the investigator (or designee), one of these signs or symptoms is more severe than expected and therefore a separate AE assessment is indicated.

9.3.4.8 Recording and Reporting of Serious Adverse Events

All SAEs, regardless of severity and causality, that occur from signing of the ICF through the last study visit or 14 days after the last dose of study drug, whichever is later, must be reported immediately and not later than within 24 hours of knowledge of the event by the investigator (or designee) on the SAE eCRF.

Serious AE reports must include at least the following information:

- Patient identification information (study number, site number, initials, and date of birth [as per local country requirements for data protection])
- The event term. Provide the diagnosis term, if known. If a diagnosis is unknown, provide the signs/symptoms and update the event term once a diagnosis is known
- The date of onset
- The last study drug administration date prior to the SAE
- Actions taken to treat the event (i.e. treatment medications, temporary discontinuation)
- Serious criteria
- The relationship of the event to the study drug or to the study procedure (e.g. the investigator's [or designee's] assessment of causality)
- A brief narrative of the SAE

Follow-up reports to already reported SAEs should contain any new information or query responses and must be documented on the SAE eCRF using the same process and timelines as for the initial SAE report.

9.3.4.9 24-Hour Emergency Contact

In a study-related medical emergency situation, when the assigned medical monitor cannot be reached, an on-call physician can be reached 24 hours per day, 7 days per week.

CCI [redacted]	

9.3.4.10 Reporting of Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE experienced by a patient for which the nature or severity of which is not expected per the applicable product information (e.g. the Investigator's Brochure for an unauthorised investigational product or summary of product characteristics for an authorised product). The safety

information for A3907 is located in the reference safety information section of the current Investigator's Brochure.

The sponsor and/or its designee are responsible for reporting SUSARs to regulatory authorities, central ethics committees, and investigators (or designees) within required timelines.

The investigator (or designee) is responsible for submitting required safety information to their local IRB or IEC per local regulations.

9.3.5 Laboratory Assessments

Clinical safety laboratory evaluations (Table 2) will be performed by a central laboratory. Samples will be collected for clinical laboratory evaluations at timepoints indicated in Table 1. All samples will be processed and transported per instructions in the laboratory manual.

Table 2 Laboratory Parameters

Clinical Chemistry	Hematology	Urinalysis
• Albumin • Alanine aminotransferase (ALT) • Alkaline phosphatase (ALP) • Aspartate aminotransferase (AST) • Bilirubin – total and conjugated • Blood urea nitrogen (BUN) • Calcium • Chloride • Creatinine • Creatine phosphokinase • Gamma-glutamyl transferase (GGT) • Lactate dehydrogenase • Potassium • Sodium • Low-density lipoprotein cholesterol (LDL-C)	• Haematocrit • Haemoglobin • Platelet count • Red blood cell count • White blood cell count and differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes) **Coagulation** • Prothrombin time • Activated partial thromboplastin time • Thrombin time	• Blood • Glucose • Ketones • Leukocytes • Nitrites • pH • Protein • Oxalate

Note: pharmacodynamic laboratory parameters are detailed in Section 9.5.

The observed values will be recorded and assessed as "normal," "abnormal not clinically significant," or "abnormal clinically significant".

For hepatic adverse events and/or hepatic decompensation, a PK sample should be collected as close to the onset of the event as possible.

Additional safety blood samples may be needed due to follow up of an abnormal value or analysis failure. The blood samples collected for safety laboratory analysis will be destroyed after the study has been completed.

9.3.6 Individual Patient Safety Monitoring

9.3.6.1 Liver Monitoring

Strategies to monitor markers of liver disease throughout the study are outlined below where the ULN will be based on central laboratory reference values. To make the distinction among the type of injury, and to make a causality assessment, the Roussel Uclaf Causality Assessment Method (Appendix 2) will be used.

For abnormalities classified as hepatic adverse events and/or hepatic decompensation, a PK sample should be collected as close to the onset of the event as possible.

If isolated transaminase elevations are observed, defined as:

Normal bilirubin AND absence of clinical hepatitis symptoms AND

- ALT or AST ≥ 5 × ULN (if normal at baseline) OR
- ALT or AST ≥ 3 × baseline (if abnormal at baseline) or > 500 U/L, whichever comes first

Then:

a. Repeat liver profile (AST, ALT, bilirubin, and prothrombin time [PT] or INR) within 2 to 3 days
b. Evaluate creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
c. As needed (for example, persistent ALT/total bilirubin elevation or worsening of liver function), consider evaluation for alternative etiologies

Monitor the patient using the close observation guidelines found below.

If any ONE of the following criteria are met:

1. Transaminases (ALT or AST ≥ 3 × baseline or 500 U/L, whichever comes first) AND bilirubin (total bilirubin > 2 × ULN) elevations
2. Transaminase elevations alone (ALT or AST > 10 × ULN or 5 × baseline or absolute threshold of 800 U/L, whichever comes first) in presence of normal LDH and CPK
3. Total bilirubin increased, unrelated to hemolysis (elevated reticulocyte count) or established genetic diseases, such as Gilbert's syndrome

a. Doubling if total bilirubin was < 3 mg/dL (equivalent to 51.3 µmol/L) at baseline OR
b. 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

4. INR increase refractory to vitamin K administration
   a. Increase by > 1.5 if INR was normal at baseline OR
   b. Increase by > 0.4 if INR was abnormal at baseline
5. 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)

Then:

a. Interrupt study medication
b. Initiate drug-induced liver injury work-up for alternative etiologies
c. Repeat liver profile (AST, ALT, total bilirubin, direct bilirubin) and PT or INR within 48 to 72 hours
d. Monitor the patient using the close observation guidelines found below.

Close Observation

For patients requiring closer observation:

- Repeat liver enzyme and serum bilirubin tests two or three times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilise or the study drug has been discontinued and the patient is asymptomatic
- Obtain a more detailed history of symptoms and prior or concurrent diseases
- Obtain a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Consider ruling out alternate etiology including acute viral hepatitis types A, B, C, D, and E; autoimmune or alcohol-associated liver disease; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtain a history of exposure to environmental chemical agents
- Obtain additional tests to evaluate liver function, as appropriate (e.g. INR, direct bilirubin)
- If the Roussel Uclaf Causality Assessment Method (RUCAM) scoring meets DILI criteria, the patient must be discontinued from the study drug.

9.3.6.2 De-challenge/Re-challenge for Liver and Clinical Hepatitis Monitoring

Re-challenge is not recommended if:

- If a patient has had possible/probable drug-induced liver injury according to RUCAM score.
- If a decompensation event has occurred (i.e. variceal haemorrhage, ascites, hepatic encephalopathy, etc.).

If an event is assessed as due to underlying cholestatic liver disease variability or another alternative aetiology is identified AND liver tests returned to baseline, re-challenge may be considered after consultation with the sponsor medical monitor.

If the ALT/total bilirubin elevations are observed after re-challenge, then repeat re-challenge is discouraged.

If a patient is permanently discontinued, monitoring should be continued as outlined in Section 9.3.6.4.

9.3.6.3 Diarrhoea

Study drug should be discontinued if a patient develops diarrhoea with at least 1 of the following concomitant signs or symptoms: grossly bloody stools, vomiting, dehydration requiring treatment with oral or intravenous rehydration and/or electrolyte imbalances, fever (≥ 38°C) and/or the diarrhoea persists for 7 or more days.

If there is gross blood in stool, INR and platelets should be measured.

Study drug will be reintroduced when the symptoms have resolved. If the diarrhoea re-occurs within 1 week after the re-challenge with no alternate etiology, the patient will be permanently discontinued and monitored as outlined in Section 9.3.6.4.

9.3.6.4 Monitoring after Permanent Discontinuation of Study Drug Due to Safety

Once study drug is permanently discontinued for hepatic, gastrointestinal (e.g. diarrhoea), or other severe AE related to study drug, the patient will be monitored weekly until the laboratory and clinical parameters have normalised/stabilised.

9.3.7 Electrocardiogram

Standard resting 12-lead ECGs will be recorded after the patient has been supine and at rest for at least 5 minutes and at least 5 minutes prior to blood sample collections at visits indicated in the Schedule of Assessments (Table 1) 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 collected.

9.3.8 Fibroscan

Where available, Fibroscan will be performed as per institution standard practice at the times indicated in the Schedule of Assessments (Table 1).

9.3.9 Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography or ECRP will be performed during the Screening Visit and is only applicable for patients without results available < 6 months prior to the Screening Period. A confirmatory MRCP is also required if a historical MRCP or ECRP is not completed within 6 months of the Screening Period.

9.3.10 MELD Score

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 − [0.025 × MELD × (140 − Na)] + 140

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 score.

9.3.11 Stool Samples

For patients with IBD, stool samples will be collected (at home) prior to each study visit beginning with Visit 2 for assessment of faecal calprotectin. Stool sampling kits will be provided to patients for at-home collection.

9.3.12 Assessment of Pruritus

At the Screening Visit, site staff will assess pruritus by having patients respond to a dichotomous yes/no question asking if they have “experienced pruritus in the past 7 days.” For patients reporting pruritus, a pruritus NRS (Appendix 1) will be completed

within the Patient Diary daily throughout the study (Table 1). The pruritus NRS contains an 11-point scale asking patients to rate their worst pruritus in the past 24 hours.

9.3.13 Assessment of Fatigue

All patients will complete a fatigue NRS (Appendix 1) within the Patient Diary daily throughout the study (Table 1).

The fatigue NRS will be used to assess fatigue daily throughout the study. The fatigue NRS contains an 11-point scale asking patients to rate their worst fatigue in the past 24 hours.

9.3.14 Assessment of Sleep Disturbance

All patients will complete a sleep disturbance NRS (Appendix 1) within the Patient Diary daily throughout the study (Table 1).

The sleep disturbance NRS will be used to assess sleep disturbance throughout the study. The sleep disturbance NRS contains an 11-point scale asking patients to rate their difficulty falling and staying asleep the previous night.

9.3.15 Assessment of Mood

All patients will complete a Likert scale (Appendix 1) in the Patient Diary daily throughout the study (Table 1).

The mood Likert scale will be used to assess mood throughout the study. The mood Likert scale contains a 5-point scale asking patients to rate their feelings of sadness or depression in the past 24 hours.

9.3.16 Special Situations

Certain safety events are defined by regulatory authorities as special situations and require reporting. These special situations include:

- Overdose of study medication (Section 9.3.17)
- Pregnancy (Section 9.3.18)
- Suspected abuse/misuse of study medication
- Medication error involving the study medication
- Drug-drug interaction

Special situations should be reported within 24 hours of awareness on the Special Situations eCRF, whether or not they result in an AE/SAE. If a Special Situation results in

an AE or SAE, the event should also be reported on the AE/SAE eCRF following the process described in Section 9.3.4.8.

9.3.17 Overdose

The no-adverse-effect dose level in the most sensitive species CCI [redacted] CCI [redacted] CCI [redacted] The risk of overdose in this study is expected to be minimal. Patients exposed to higher than proposed doses should be observed and supported appropriately.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be stopped.
- Perform PK samples until study intervention can no longer be detected systemically.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically and until AE/SAE and laboratory abnormalities resolve or stabilize.

Any overdose of study medication is to be reported within 24 hours of knowledge of the overdose on the Special Situations eCRF. Any AE/SAE that occurs as a result of an overdose is to be reported on the AE/SAE eCRF.

9.3.18 Pregnancy and Contraception

Female subjects of childbearing potential and males with female partners of childbearing potential must agree to use a highly effective contraceptive method (defined as achieving a failure rate of less than 1% per year) in combination with a barrier method from the time of the Screening Visit until week 12 visit (EOT) plus 5 half-lives after the last dose of A3907.

Acceptable forms of highly effective contraception include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation

- Progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments
    - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Barrier methods such as condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream should be combined with a highly effective contraceptive method. If a pregnancy occurs in a male patient's partner at any time during the study, the pregnancy should also be reported and followed.

Women in the following categories are considered WONCBP: premenopausal female with permanent infertility due to one of the following (for the purpose of this study):

(a) Documented hysterectomy
(b) Documented bilateral salpingectomy
(c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

(1) Postmenopausal female

(a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with a FSH level ≥ 40 mIU/mL is required.

Pregnancy is not considered to be an AE. However, if the patient has been dosed with the study drug, the pregnancy must be reported on the Pregnancy eCRF within 24 hours of site awareness (Section 9.3.4.8). Date of exposure and, as far as possible, details of the period of gestation at the time of exposure must be provided.

The pregnancy should be followed up to determine outcome, including spontaneous termination, details of birth, and presence of any birth defects, congenital anomalies, or newborn or maternal complication. An infant who was exposed in-utero will be followed for up to 2 years after delivery. Any pregnancy that occurs within 90 days of the last dose of study drug must be reported to the sponsor.

9.4 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be collected according to the schedule in Table 1. Samples for Arms 1+2 will be obtained on Day 0 (Visit 2) and Week 12 (Visit 7) pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 10 hours post-dose (± 5 minutes). Samples for Arms 3+4 will be obtained on Day 0 (Visit 2) pre-dose at 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post-dose (± 5 minutes). CCI [redacted]

CCI [redacted]

CCI [redacted] Samples for Arms 3+4 will be obtained on Day 98 (Visit 7) pre-dose and at 0.5, 1, 1.5, 2, 4, 6, 8, and 10 hours post-dose (± 5 minutes). The post-dose sample collections will be obtained post administration of the first BID dose. For Visits 3 to 6 (inclusive), PK will be collected once pre-dose, and once for Visit 8. Sampling timepoints at Week 12 (Visit 7) may be adjusted based on observed data from Day 0 (Visit 2) without changing the total number of blood samples.

All pre-dose samples should be taken immediately before the administration of study drug. Patients will fast for 4 hours before study visit (only water permitted). Blood samples will be processed for collection of plasma fractions for determination of A3907 concentrations and banked for exploratory assessment of MIST (Visit 2 and Visit 7 only). In addition, a blood sample for PK analysis should be collected, if possible, at the time of any SAE.

A PK sample collection manual will be provided to instruct the type of anticoagulant, material supplies, and sample processing, storage, and shipping procedures. Plasma samples will be shipped to the analytical laboratory for analysis.

9.5 Pharmacodynamic Assessments

9.5.1 Bile Acids

Blood samples for analysis of individual and total serum bile acids will be drawn at all study visits from Visit 1 through Visit 8.

Urine samples for analysis of individual and total bile acids will be collected by the patient during the 24-hour period prior to Visits 2, 3, 5, 7, and 8. Instructions for the urine collection can be found in the laboratory manual.

For any visit at which a bile acid sample result is unreportable, an additional unscheduled visit for a repeat sample collection may be scheduled. Samples will be handled, stored, and transported to a central laboratory per instructions in the laboratory manual.

9.5.2 Serum Biomarkers

Biomarkers of liver fibrosis will be assessed, including autotaxin, ProC3, hsCRP, MMP7, MMP9, ELF score, and CA 19-9. Bile acid synthesis biomarker, C4, and FGF-19 will also be assessed. Blood samples for biomarker assessment will be collected according to Table 1; samples for autotaxin, C4, and FGF-19 are to be obtained once per applicable visit, pre-dose. Details of sample handling, storage, and transportation to a central laboratory will be provided in the laboratory manual.

10 STATISTICAL EVALUATION

10.1 Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. Approximately 24 patients are planned to be enrolled into the study.

10.2 Statistical Methods

10.2.1 Statistical Analysis Sets

Safety Analysis Set

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

Pharmacokinetic Analysis Set

The PK analysis set will include all patients who received at least 1 dose of A3907 and have evaluable PK data. The PK analysis set will be used for all PK analyses.

Pharmacodynamic Analysis Set

The PD population will include all patients who received at least 1 dose of A3907 and for whom at least 1 PD marker can be evaluated. The PD analysis set will be used for all PD analyses.

10.2.2 Methods of Statistical Analyses

10.2.2.1 General Principles

Descriptive statistics will mainly be used in this open-label study. All statistical analyses will be performed using SAS version 9.3 or higher.

In general, continuous data will be summarised using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarised using the count and percentage of patients.

10.2.2.2 Missing Data

Missing data will be reported descriptively. In general, imputations of missing observations will not be made. Any additional analysis concerning missingness and details regarding handling of missing data will be described in the statistical analysis plan (SAP).

10.2.2.3 Demographic and Baseline Characteristics

Descriptive summaries of demographics and other baseline characteristics, including medical and surgical history, will be presented overall using the safety analysis set. Prior medication will be summarised overall using the safety analysis set.

10.2.2.4 Patient Disposition

The following will be summarised overall by treatment arm:

- Patients enrolled (who signed the informed consent)
- Patients treated
- Patients discontinuing the treatment permanently (including reason for discontinuation)
- Patients completing the study
- Patients withdrawing early (including withdrawal reason)

Additionally, patients enrolled, included in the safety analysis set will be summarised by region by treatment arm.

10.2.2.5 Safety Analysis

Safety data will be analyzed using descriptive statistics and overall summaries of AEs, SAEs, ECG, vital signs, physical examinations, clinical laboratory tests (hematology, clinical chemistry, urinalysis, and coagulation), and concomitant medication. Analyses will be performed using the safety analysis set.

Summaries of AEs (coded according to Medical Dictionary for Regulatory Activities [MedDRA] system organ class and preferred term) will include:

- Overview of the incidence of all AEs (AEs, Drug-related AEs, AEs leading to study discontinuation),
- TEAEs by system organ class (SOC) and preferred term (TEAEs, Drug-related TEAEs, TEAEs leading to study discontinuation),
- Intensity/severity of TEAEs by SOC and preferred term,
- Drug-related TEAEs by SOC and preferred term,
- TEAEs leading to study discontinuation by SOC and preferred term, and
- Treatment-emergent SAEs by SOC and preferred term.

Summaries of TEAEs will be presented separately by the single dose (Day 0 to Day 13) and 12-week (Day 14 to Day 112) treatment periods.

Concomitant medication use during the Treatment Period will be summarised by Anatomical Therapeutic Chemical (ATC) class and World Health Organization (WHO) preferred name.

Summaries of vital signs and clinical safety laboratories will be presented. For each visit, the actual results, the change from baseline, and the number and percentage of patients with potentially clinically significant values observed post-baseline will be presented.

Data listings will be provided for each patient for all safety parameters.

10.2.2.6 Compliance and Exposure

Treatment Compliance = 100 × ([Number of study drug dispensed – number of study drug returned]/number of study drug that should be taken).

10.2.2.7 Pharmacokinetic Analysis

The PK analysis will be conducted employing noncompartmental methods using WinNonlin®. Only patients who are given A3907 and have evaluable plasma concentration-time profiles will be included in the analysis.

Individual A3907 plasma concentrations at specified timepoints will be listed for each patient and will be summarised by dose level. Individual plasma concentration-time profiles of A3907 will be plotted on both a linear and a semi-logarithmic scale for each dose level. Mean values will also be presented graphically for each dose level.

The following PK parameters may be determined for A3907 unless otherwise specified:

- C_{max}: Maximum plasma concentration
- T_{max}: Time of maximum plasma concentration
- $t_{½}$: Elimination half-life
- AUC_{0-t}: Area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration)
- AUC_{inf}: Area under the plasma concentration-time curve from time zero to infinity

Additional details on the computation of the PK parameters will be provided in a separate analysis plan. Analysis and results of potential exploratory analyses of A3907 metabolites in plasma samples will be reported outside the Clinical Study Report for the study.

10.2.2.8 Pharmacodynamic Analysis

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 change from baseline will be analyzed in addition to the actual visit values. For categorical data, shift tables or frequency and percentages of patients will be presented as appropriate.

Details on evaluation of exploratory analyses of potential PD biomarkers will be described in the SAP.

10.2.3 Exploratory Analysis

All exploratory endpoints, except for PD endpoints, will be summarised descriptively based on the safety analysis set.

10.2.4 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.

10.2.5 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 3 patients have completed 2 weeks of treatment in Arm 1 to determine if enrollment in Arm 2 may occur. The SRC will review safety and PK data after at least 3 patients have completed 2 weeks of treatment in Arm 2 to determine if enrollment 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.

11 DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review and regulatory inspection.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Conduct of the Study

Albireo AB/designee shall implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with United States Food and Drug Administration (FDA) regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The investigator (or designee) may not deviate from the protocol without a formal protocol amendment having been established and approved by the competent authority, as applicable, and IEC/IRB, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be withdrawn from the study and render that patient non-evaluable.

12.2 Study Monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, an Albireo AB, representative or designee will review the protocol and eCRF with the investigators (or designees) and the investigative staff. During the study, the clinical monitor (clinical research associate [CRA]) will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The investigator (or designee) must ensure that eCRFs are completed within a timely period of the patient visits, as per individual site agreements, and must allow the CRA and Albireo AB, representative or designee periodic access to patient records and all study -related materials, including relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the study centre. Albireo AB, monitoring standards require full verification for the presence of the signed ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of primary efficacy and safety variables.

The CRA will review source data compared with the eCRFs and will verify source data according to the study specific- monitoring plan. The design of the study, the frequency of patient visits, and the site enrollment rate will determine the frequency of monitoring visits. Upon study completion, the CRA will visit the site to conduct a study termination visit, which will include collection of any outstanding documentation.

It is recommended that the investigator/investigative staff log into the eCRF system every working day or at minimum twice weekly in order to provide a prompt response to queries. The investigator/investigative staff should respond to queries and make any relevant changes to the study data within 3 working days.

13 ETHICS

13.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator (or designee) is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB and competent authority, as applicable. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH, GCP and local requirements, as applicable.

The IEC/IRB and regulatory authority (competent authority), as applicable, shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures (e.g. advertisements), written information to be provided to the patients, IB, available safety information, information about payment and compensation available to patients and caregivers, the investigator's (or designee's) curriculum vitae, and/or other evidence of qualifications and any other documents requested by the IEC/IRB or competent authority, as applicable.

In the European Union (EU), this study shall be conducted in compliance with the EU Regulation No 536/2014. The sponsor will take steps to ensure that the Investigators/Institutions have necessary technical and organizational arrangements to follow the applicable rules on protection of personal data to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data; that the Investigators/Institutions have the necessary processes in place to ensure confidentiality of records and personal data of subjects; and that the Investigators/Institutions have the necessary measures in place in case of a data security breach.

13.2 Written Informed Consents

The investigator (physician) or investigative staff will, according to local regulation, explain to each patient (or legally authorised representative) the nature of the study, its purpose, the procedures involved, the expected duration, alternative treatment, the potential risks and benefits involved, and any discomfort that may occur. Each patient will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Patients will be informed that they may experience side effects or be at risk for symptoms, illnesses, or complications that cannot be foreseen by Albireo AB. Patients will be advised that study procedures include regular blood sampling for measurement of safety parameters and biological markers and that some minor risks are associated with these procedures.

Informed consent should be given by means of a signed ICF, written in non-technical language in accordance with ICH GCP, the Declaration of Helsinki, and regulatory authorities. The patient should read and consider the statements before signing and dating them and should be given a copy of each signed document. If written consent is not possible, oral consent can be obtained if witnessed and followed by a signed statement from one or more persons not involved in the study, indicating why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained.

The ICF is part of the protocol and must be submitted by the investigator/investigative staff with the protocol for IEC/IRB approval. Albireo AB will supply an ICF which complies with regulatory requirements and country laws and is considered appropriate for the study. Any changes to the ICF suggested by the investigator (or designee) must be agreed to by Albireo AB before submission to the IEC/IRB and a copy of the approved version must be provided to the clinical monitor after IEC/IRB approval.

14 DATA HANDLING AND RECORD KEEPING

14.1 Case Report Forms/Source Data Handling

The investigator (or designee) shall be provided with standardised eCRFs and shall ensure that all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator (or designee) must sign each eCRF to verify the integrity of the data recorded.

A list of normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. As a central laboratory has been selected to conduct bile acid tests, it is essential that all bile acid samples be analyzed at that laboratory.

The investigator (or designee) must maintain source documents such as laboratory reports, consultation reports, and complete medical history and physical examination reports.

14.2 Retention of Essential Documents

Essential documents, as defined by ICH GCP, include: the signed protocol and any amendment(s); copies of the completed eCRFs (for site archiving, compact discs of eCRF data for specific patients will be provided); signed ICFs; hospital records and other source documents; IEC/IRB approvals and all related correspondence including approved documents; drug accountability records; study correspondence; and a list of patients' names and addresses.

The investigator/investigative staff must retain copies of these essential documents for the period specified by ICH GCP and by applicable regulatory requirements. The investigator/investigative staff will inform Albireo AB, of the location where the essential documents are stored and must contact Albireo AB, for approval before disposing of any essential documents. The investigator/investigative staff should take measures to prevent accidental or premature destruction of these documents.

14.3 Organisational and Technical Arrangements for Personal Data Protection

In compliance with Regulation (EU) No 536/2014 (Clinical Trial Regulation) and Regulation (EU) 2016/679 (General Data Protection Regulation), all study sites in Europe and vendors supporting the study are required to maintain and enforce security policies, standards, and procedures designed to secure Personal Data and other data to which their

employees have access. The core technical and organisational security controls to be implemented by sites and vendors include:

- **Data Access Controls**: Personal Data may only be accessed, used, copied, modified, or deleted by authorised personnel for the purposes described in the contract (e.g. role-based access provision).
- **Logical Access Controls**: Procedures will be in place to prevent unauthorised access to Personal Data that is stored on computer systems (e.g. secure passwords, multifactor authentication, system monitoring).
- **Physical Access Controls**: Procedures will be in place to prevent unauthorised access to physical locations where Personal Data is processed (e.g. office entry controls and monitoring, locking file shelves and computer screens when absent).
- **Data Transfer Controls**: Procedures will be in place to prevent Personal Data from being accessed, copied, modified, or deleted without authorisation during electronic transmission or transport (e.g. encrypting data during transfer), as well as to identify and verify recipients of and transferred Personal Data.
- **Network Controls**: Network security will be maintained using commercially available equipment and industry standard techniques, including firewalls, intrusion detection and/or prevention systems, access control and routing protocols.
- **Policy and Procedure Controls**: Security and Incident Response Policies (including Personal Data Breach) are required.
- **Availability and Risk Controls**: Procedures will be in place to react to risks that are associated with the Processing of Personal Data (e.g. accidental or unlawful destruction, loss, or alteration, unauthorised or unlawful storage, processing, access or disclosure of Personal Data). This includes procedures to:
    - ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;
    - restore the availability and access to Personal Data in a timely manner in the event of a physical or technical incident;
    - regularly test, assess, and evaluate the effectiveness of technical and organisational procedures for ensuring the security of the processing of Personal Data;
    - identify vulnerabilities with regard to the processing of Personal Data in systems used to provide services to Affiliates.
- **Workforce Controls**: Appropriate background checks will be conducted for job applicants to limit risks associated with employee confidentiality and security. A

security awareness program will be implemented to train personnel about their security obligations. This program includes training about logical and physical security controls and security incident and Personal Data Breach policies and procedures.

15 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate agreement.

16 PUBLICATION POLICY

Albireo AB will retain the ownership of all data. When the study is complete, Albireo AB shall arrange the analysis, tabulation of data, and preparation of a clinical study report. Albireo AB may also use the data for publication, presentation at scientific meetings, and submission to regulatory authorities. All proposed publications based on this study must be subject to the sponsor's approval requirements.

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18 APPENDICES

Appendix 1 Numerical Rating Scales

1.	Have you experienced itch due to your liver condition in the past 7 days?	□ Yes □ No

1.	How bad was your worst itching in the past 24 hours?	No itching at all	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible itching
2.	How bad was your worst feeling of fatigue (lack of energy, tiredness) in the past 24 hours	No fatigue at all	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Worst possible fatigue
3.	How difficult was it for you to fall asleep last night?	Not difficult at all	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Extremely difficult
4.	How difficult was it for you to stay asleep last night?	Not difficult at all	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Extremely difficult
5.	How often did you feel sad or depressed in the past 24 hours?	☐ Never ☐ Almost never ☐ Sometimes ☐ Often ☐ Always	

NRS Scale:
NRS = 0 – no itching/fatigue/sleep disturbance
NRS < 3 – mild itching/fatigue/sleep disturbance
NRS ≥ 3 < 7 – moderate itching/fatigue/sleep disturbance
NRS ≥ 7 < 9 severe itching/fatigue/sleep disturbance
NRS ≥ 9 – very severe itching/fatigue/sleep disturbance

Appendix 2 Roussel Uclaf Causality Assessment Method

RUCAM Causality Assessment

Drug: _____ Initial ALT: _____ Initial Alk P: _____ R ratio = [ALT/ULN] ÷ [Alk P/ULN] = ___ ÷ _____ = _____

The R ratio determines whether the injury is hepatocellular (R > 5.0), cholestatic (R < 2.0), or mixed (R = 2.0 – 5.0)

	Hepatocellular Type		Cholestatic or Mixed Type		Assessment
1. Time to onset					
	Initial Treatment	**Subsequent Treatment**	**Initial Treatment**	**Subsequent Treatment**	**Score** (check one only)
○ From the beginning of the drug: • Suggestive • Compatible	 5 – 90 days < 5 or > 90 days	 1 – 15 days > 15 days	 5 – 90 days < 5 or > 90 days	 1 – 90 days > 90 days	 +2 +1
○ From cessation of the drug: • Compatible	 ≤ 15 days	 ≤ 15 days	 ≤ 30 days	 ≤ 30 days	 +1
Note: If reaction begins before starting the medication or >15 days after stopping (hepatocellular), or >30 days after stopping (cholestatic), the injury should be considered unrelated and the RUCAM cannot be calculated.					
2. Course	**Change in ALT between peak value and ULN**		**Change in Alk P (or total bilirubin) between peak value and ULN**		**Score** (check one only)
After stopping the drug:					
• Highly suggestive	Decrease ≥ 50% within 8 days		Not applicable		+3
• Suggestive	Decrease ≥ 50% within 30 days		Decrease ≥ 50% within 180 days		+2
• Compatible	Not applicable		Decrease < 50% within 180 days		+1
• Inconclusive	No information or decrease ≥ 50% after 30 days		Persistence or increase or no information		0
• Against the role of the drug	Decrease < 50% after 30 days **OR** Recurrent increase		Not applicable		-2

○ **If the drug is continued:** • Inconclusive	All situations	All situations	0
3. Risk Factors:	**Ethanol**	**Ethanol or Pregnancy (either)**	**Score** (check one for each)
○ Alcohol or Pregnancy	Presence Absence	Presence Absence	+1 0
○ Age	Age of the patient ≥ 55 years Age of the patient < 55 years	Age of the patient ≥ 55 years Age of the patient < 55 years	+1 0

4. Concomitant drug(s):		**Score** (check one only)
○ None or no information or concomitant drug with incompatible time to onset		0
○ Concomitant drug with suggestive or compatible time to onset		-1
○ Concomitant drug known to be hepatoxic with a suggestive time to onset		-2
○ Concomitant drug with clear evidence for its role (positive rechallenge or clear link to injury and typical signature)		-3
5. Exclusion of other causes of liver injury:		**Score** (check one only)
Group I (6 causes): ○ **Acute viral hepatitis** due to **HAV** (IgM anti-HAV), or ○ **HBV** (HBsAg and/or IgM anti-HBc), or ○ **HCV** (anti HCV and/or HCV RNA with appropriate clinical history) ○ **Biliary obstruction** (By imaging) ○ **Alcoholism** (History of excessive intake and AST/ALT ≥ 2) ○ **Recent history of hypotension, shock or ischemia** (within 2 weeks of onset) **Group II (2 categories of causes):** ○ Complications of underlying disease(s) such as autoimmune hepatitis, sepsis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis; or ○ Clinical features or serologic and virologic tests indicating acute CMV, EBV, or HSV.	○ All causes in Group I and II ruled out	+2
	○ The 6 causes of Group I ruled out	+1
	○ Five or 4 causes of Group I ruled out	0
	○ Less than 4 causes of Group 1 ruled out	-2
	○ Non-drug cause highly probable	-3
6. Previous information on hepatotoxicity of the drug:		**Score** (check one only)
○ Reaction labeled in the product characteristics		+2

○ Reaction published but unlabeled			+1
○ Reaction unknown			0
7. Response to readministration:			**Score** (check one only)
○ Positive	Doubling of ALT with drug alone	Doubling of Alk P (or bilirubin) with drug alone	+3
○ Compatible	Doubling of the ALT with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	Doubling of the Alk P (or bilirubin) with the suspect drug combined with another drug which had been given at the time of onset of the initial injury	+1
○ Negative	Increase of ALT but less than ULN with drug alone	Increase of Alk P (or bilirubin) but less than ULN with drug alone	-2
○ Not done or not interpretable	Other situations	Other situations	0
		TOTAL (add the checked figures)	

PPD

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