Clinical Trial Protocol: APD334-010

Study Title:	An Open-label, Pilot, Proof of Concept Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Etrasimod (APD334) in Patients with Primary Biliary Cholangitis
Study Number:	APD334-010
Study Phase:	2
Product Name:	Etrasimod (APD334)
EudraCT Number:	NA
Indication:	Primary Biliary Cholangitis
Investigators:	Multicenter
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121 United States
Sponsor Contact:	[redacted], MD, MHS [redacted] Research and Development & CMO Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121 US Tel: [redacted] Email: [redacted]
Medical Monitor	[redacted], MD Medical and Safety [redacted] Arena Pharmaceuticals, Inc. Gotthardstrasse 3 CH – 6300 Zug Switzerland Tel: [redacted] Email [redacted]

Original Protocol:	26 April 2017
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

[redacted]

LIST OF IN-TEXT FIGURES

SYNOPSIS

Protocol Number:	APD334-010
Name of Drug:	Etrasimod (APD334)
Title:	An Open-label, Pilot, Proof of Concept Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Etrasimod (APD334) in Patients with Primary Biliary Cholangitis
Indication:	Primary Biliary Cholangitis (PBC)
Study Phase:	Phase 2
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121, United States
Name of Sponsor Contact:	[redacted], MD, MHS [redacted] Research and Development & CMO Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121, US Tel: [redacted] Email: [redacted]
Name of Principal Investigator(s):	Multicenter
Medical Monitor:	[redacted], MD Medical and Safety [redacted] Arena Pharmaceuticals, Inc. Gotthardstrasse 3 CH – 6300 Zug Switzerland Tel: [redacted] Email: [redacted]
Test Product, Dose and Mode of Administration:	Etrasimod 1 mg tablet per os (p.o.) with possible dose escalation to 2 mg p.o., based on available pharmacokinetic (PK) and safety data (vital signs and electrocardiogram [ECG]). [redacted]

	[redacted]
Background	Etrasimod is an orally available, selective, sphingosine 1-phosphate 1 ($S1P_1$) receptor modulator. S1P is a signaling sphingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. The $S1P_1$ receptor is a physiological mediator that has been shown to regulate lymphocyte recirculation between lymphoid tissue and blood. Binding and internalization of the $S1P_1$ receptor may result in lymphocyte retention within lymphoid tissue, with subsequent reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. $S1P_1$ receptor surface expression is required for S1P gradient-mediated lymphocyte migration out of lymphoid tissue into the circulation[1]. Modulators of the $S1P_1$ receptor, such as etrasimod, block lymphocyte migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes [1]. Recent clinical development of $S1P_1$ receptor modulators has demonstrated their effect on resulting lymphocyte sequestration, and their potential for treating multiple autoimmune and chronic inflammatory diseases. *Rationale for use of etrasimod in treatment of PBC* Histologically, PBC is characterized by florid bile duct lesions with damage to biliary epithelial cells, dense portal inflammatory infiltrate and progressive loss of small intrahepatic bile ducts. T cells are important players in the pathogenesis of PBC. The disease results from a chronic inflammatory process in which T cells attack the small bile duct epithelial cells. These epithelial cells eventually disappear, causing cholestasis and further progression of PBC. The T cells seem to be of both CD4+ and CD8+ origin, as shown by immunohistochemical staining in portal and periportal areas [2]. The trigger of this autoimmune disease is unknown, but genome-wide association studies have suggested the importance of certain HLA variants and other immune-related genes, such as components of the IL-12 signaling cascade. Furthermore, more than 95% of patients also develop a humoral autoimmune response to mitochondrial proteins (i.e., antimitochondrial antibodies, AMA) [2,3]. The reduced peripheral lymphocyte availability seen with the $S1P_1$ modulator etrasimod is expected to decrease both CD4+ and CD8+ T cell recruitment to sites of inflammation, such as around the bile ducts. In addition to $S1P_1$ modulation, the

	activation of $S1P_4$ and $S1P_5$ receptors may confer additional immunomodulatory effects that could translate into efficacy for the treatment of PBC. NK cells appear to be involved in the pathogenesis of PBC: their levels are increased in blood and liver of patients with strong cytotoxic activity against biliary epithelial cells[4], and resting as well as activated NK cells express $S1P_1$, $S1P_4$ and $S1P_5$ receptors. The $S1P_5$ receptor has been reported to be involved in chemotaxis of NK cells [5]. Other cells that may be potentially blocked by etrasimod include neutrophils, which were recently observed to be S1P4 dependent [6]. Compared with other $S1P_1$ receptor modulators such as fingolimod, etrasimod has shown overall more selective activation of $S1P_1$, $S1P_4$ and $S1P_5$ receptors[7] and may thus represent a novel and suitable approach for treating patients with PBC.
Objectives:	**Primary objective:** Safety • To assess the safety and tolerability of etrasimod in patients with PBC. **Secondary objectives:** Efficacy and PK • To evaluate the efficacy (i.e., changes in alkaline phosphatase [ALP] levels from baseline) of etrasimod in patients with PBC. • To assess single dose and steady-state PK of etrasimod in patients with PBC. **Exploratory objectives:** • To assess the pharmacodynamic (PD) response (lymphocyte counts and subsets thereof). • To assess serum high sensitivity C-reactive protein (hsCRP), alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), AMA, [redacted] total IgG and IgM, [redacted] and 7-alpha hydroxy 4-cholesten-3- one (C4). • To assess quality of life (QoL) and incidence of pruritus and fatigue. • [redacted] • To assess changes in Schirmer [redacted] tests in patients with abnormal results at screening.
Study Design	This pilot, open-label, single arm, proof of concept, multicenter study will evaluate orally administered etrasimod for 24 consecutive weeks in PBC patients who had an inadequate response to ursodeoxycholic acid (UDCA).

	The screening period will last 5 to 8 weeks and will be followed by a 24-week treatment period, which includes assessment of safety, PK, tolerability and efficacy in up to 20 patients. During the treatment period, patients will need to take 1 tablet of study medication once per day (q.d.). The last dose is planned to be taken one day before the end of the treatment period (during Week 24). A follow-up visit will take place 2 weeks after the end of treatment. Please refer to the Schedule of Procedures and Visits (Table 1) for the detailed plan. Screening Period (5 to 8 weeks before baseline visit): Each patient will be asked to visit the study site at least 2 times for screening assessments within the 8 weeks prior to the planned start of the treatment (Day 1). Screening Visit 1 is to occur between Week -8 and Week -5. Screening Visit 2 is to occur at least 4 weeks from Screening Visit 1. For patients with ALP, ALT, AST, or total bilirubin values from Screening Visits 1 and 2 that are not within 20% of each other (see Inclusion Criterion 9), an unscheduled visit within the screening period may be conducted to repeat these assessments. All patients must be consented before any study specific procedure is performed and written informed consent must be obtained. Patients will then undergo screening procedures to determine eligibility. [redacted] Treatment period (24 weeks): Patients will come to the clinic [redacted]. Vital signs and ECG changes will be monitored extensively during this time, and PK sampling will be performed (6.13). Patients will receive a 1 mg etrasimod tablet (p.o., q.d.) from Day 1 onwards. If the 1 mg dose is well tolerated and there are no clinically significant changes in vital signs and ECG, the 1 mg dose level will be maintained. If 1 mg is not tolerated, then treatment will be stopped per the dose-stopping rules (see below). The 1 mg dose level may be increased to 2 mg at Week 12, based on the patient's safety and PK data. This data will be reviewed by a safety and dose escalation committee who will decide whether or not to proceed with 2 mg treatment. Patients with dose escalation on Week 12 will have PK sampling [redacted] (6.13), and vital signs and ECG monitoring performed [redacted] Visits [redacted]: Patients will return to the study site and all planned examinations as described in Schedule of Procedures and Visits (Table 1) will be conducted. [redacted] only dose escalated patients will visit. Last dose of

	study medication is planned 1 day before the end of the treatment visit at Week 24. Follow-up Visit/End of Study Visit: *Visit Week 26, 2 weeks after end of treatment:* Patients will return to the study site for the final visit, and final procedures will be performed per Schedule of Procedures and Visits (Table 1). *Premature Discontinuation:* All procedures planned for Weeks 24 and 26 visits should be performed for all patients who discontinue the study prematurely.
Dose-stopping Rules:	Any of the following findings in a patient during treatment will lead to a stop in etrasimod dosing in the affected patient: 1. Certain ECG changes (see details in text below), **or** 2. Clinical evidence of drug-induced liver injury (DILI; as described in 6.15) As described in the study plan above, at the discretion of the PI, the dose of etrasimod may be adjusted from 2 mg q.d. back to 1 mg q.d. if deemed necessary. If the patient is on 1 mg, the PI may discontinue etrasimod treatment if deemed necessary based on the dose-stopping rules. Close Observation for Possible DILI: It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. Close observation is mandatory for any study subject who meets one or more of the following "possible DILI" laboratory criteria: • ALT or AST that is <ULN at baseline, followed by ALT or AST increase to >3 × ULN • ALT or AST that is >ULN at baseline, followed by ALT or AST increase to >2 × baseline • ALP >2 × baseline • Total bilirubin >1.5 × ULN Close observation includes: • Repeating liver enzyme and serum bilirubin tests within 48-72 hours. Then, repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities resolve, abnormalities stabilize, or the study drug has been discontinued and the subject is asymptomatic. • Obtaining a more detailed history of symptoms and prior or concurrent diseases.

- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering consultations, imaging studies, and/or therapeutic interventions, as required.

<u>Study Drug Discontinuation for Suspected DILI:</u>

Should any patient who meets "possible DILI" laboratory criteria have persistence or worsening of lab data (i.e., ALT, AST, ALP, and/or total bilirubin) after one week of close observation, study drug must be discontinued. In addition, immediate study drug discontinuation is mandatory for any study patient who meets one or more of the following "suspected DILI" clinical criteria:

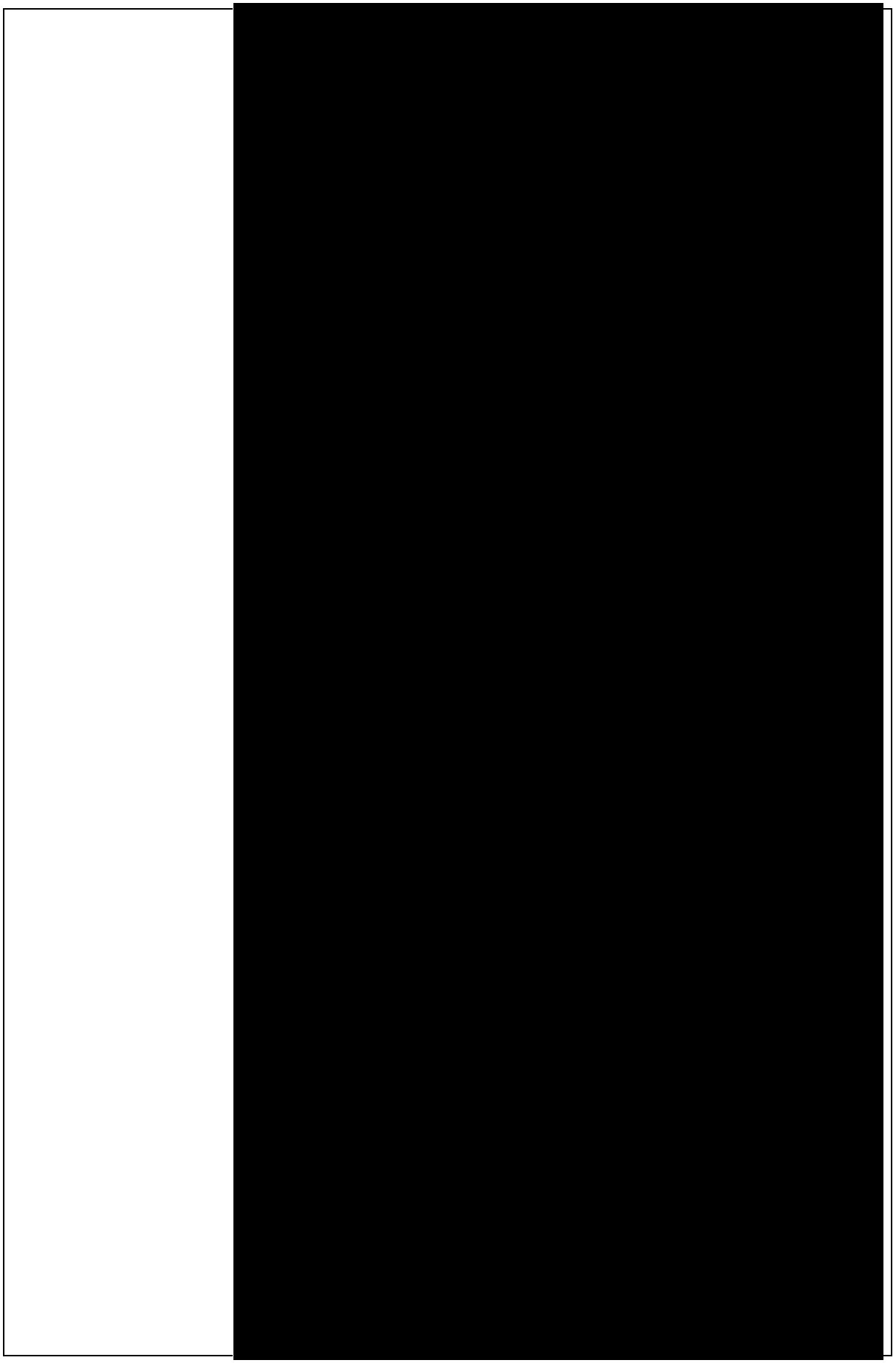
- ALT or AST <2 × ULN at baseline, followed by ALT or AST increase to >5 × baseline
- ALT or AST ≥2 × ULN but <5 × ULN at baseline, followed by ALT or AST increase to >3 × baseline
- ALT or AST increase to >2 × baseline AND concomitant total bilirubin increase to >2 × baseline
- ALT or AST increase to >2 × baseline AND concomitant INR increase >0.2
- Clinical signs and symptoms of liver inflammation, including but not limited to fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, jaundice, icterus, and/or eosinophilia (>5%)

<u>ECG changes:</u>

Safety ECGs will be recorded on an ECG machine (12-lead), they will be printed and reviewed on-site by the PI or another physician (e.g., cardiologist). Typically, all safety ECGs will be obtained as single tracings, except for the pretreatment ECG obtained on Day 1, which is a triplicate recording.

	[redacted]
Study Site(s):	Multicenter.
Study Population:	Patients with confirmed PBC diagnosis who fulfill the eligibility criteria.
Inclusion Criteria:	Inclusion and exclusion criteria that refer to an assessment being performed "at screening" are referring to Screening Visit 1 unless specified otherwise. 1. Males or females aged 18 to 80 years (inclusive) at the time of screening, with confirmed PBC diagnosis based upon at least 2 of 3 criteria: • AMA titer >1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies (anti-GP210 and/or anti-SP100) • ALP >1.5 × ULN for at least 6 months • Liver biopsy findings consistent with PBC

	2. Use of UDCA for at least 6 months prior to screening (stable dose for at least 3 months immediately prior to screening) [redacted] 4. Patients must have the following laboratory parameters at screening • ALP >1.5 × ULN but <10 × ULN (at all screening visits) • ALT and AST <5 × ULN (at all screening visits) • Total bilirubin <ULN (at all screening visits) [redacted]



	[redacted] 8. AST, ALT, ALP, and total bilirubin must have 2 values at least 4 weeks apart that are within 20% of each other.
Exclusion Criteria	1. Chronic liver disease of a non-PBC etiology. However, PBC patients accompanied with primary Sjögren's syndrome (pSS) are eligible to be enrolled. 2. History or evidence of clinically significant hepatic decompensation: [redacted] 3. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) [redacted] 7. Infection with hepatitis C virus anytime in the past; confirmed active infection with hepatitis B virus at screening.

	[redacted]
	13. Treatment with obeticholic acid (OCA) or fibrates (including bezafibrate) within 30 days prior to Day 1. 14. Other immunosuppressive, immunomodulating or antineoplastic agents not listed in Permitted Medications section (6.17.1) within 30 days prior to Day 1 (or not meeting the stability time period for concomitant medications indicated as permitted).
	[redacted]

	[redacted]
Duration of the Study (per Patient):	Up to 34 weeks total: with 5 to 8 weeks for screening, followed by a 24-week treatment period (including a 12-week 1 mg treatment period followed by a 12-week 2 mg treatment period if

	tolerable) and a follow-up visit 2 weeks after the end of treatment.
Sample Size:	Up to 20 patients total
Efficacy Endpoints:	• Change from baseline to Week 12 and 24 in serum ALP concentration. • Change from baseline to Week 12 and 24 in: ○ Complete blood counts (including lymphocytes and subset thereof). ○ hsCRP, ALT, AST, GGT, [redacted] C4 and [redacted] serum concentrations. ○ Total serum IgG, IgM, and AMA. ○ QoL, pruritus and fatigue (using PBC-40 and 5-D pruritus scales). ○ Ophthalmological examinations: ▪ The Schirmer Test ▪ [redacted] Test in patients with abnormal results at screening
Safety Assessments:	The following will be captured to assess the safety endpoints: - Clinical laboratory tests, including hematology, serum chemistry, coagulation, and urinalysis - [redacted] - Vital sign measurements - [redacted] - Safety 12-lead ECG - Physical and neurological examination - Adverse event reporting
Pharmacokinetic Assessments	Patients will have a serial PK sampling [redacted] All PK samples are to be collected [redacted] of the scheduled timepoint.

	PK data [redacted] will support the dose escalation of etrasimod in PBC patients at Week 12. An additional PK blood sample will be collected, if possible, at the time of any intolerable AE or SAE. Samples will be analyzed for etrasimod and its putative metabolites (if possible). After the completion of study, samples will be transferred to sponsor designated storage site in US, and retained for future exploratory research related to the study drug. In general, the storage time is no more than 3 years.
Statistical Analyses:	There is no formal sample size estimation for this proof-of-concept open label study. A sample size of up to 20 patients is reasonable to assess the efficacy and safety of etrasimod in the target population. An interim analysis of safety and efficacy may be performed when up to half of patients have finished 12 weeks of treatment. Pharmacokinetic parameters will be calculated using non-compartmental methods. [redacted] Summary statistics and appropriate graphic displays will be provided for PK and PD parameters, biomarkers and efficacy (ALP changes). Safety information after administration of etrasimod will be evaluated by tabulating adverse events and clinical assessment of clinical laboratory data by treatment period and follow up period. Confidence interval of key efficacy measures will be also produced for non-inferential comparisons with published data. Exploratory analysis of main study endpoints may be performed in subset of patients of medical interests, such as patient demographics, baseline ALP levels, baseline disease characteristics, biomarker, previous disease treatment received, etc. [redacted]
Date	**27 June 2018**

LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AMA	anti-mitochondrial antibodies
ANA	anti-nuclear antibodies
AST	aspartate aminotransferase (SGOT)
AV	atrio-ventricular
bpm	beats per minute
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CRP	C-reactive protein
CRO	contract research organization
D	Day
DILI	drug-induced liver injury
ECG	Electrocardiogram
ED50	half maximal dose
[redacted]	[redacted]
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
[redacted]	[redacted]
FU	follow up
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HBsAg	hepatitis B surface antigen
[redacted]	[redacted]
HCV	hepatitis C virus
HREC	human research ethics committee (AUS)
[redacted]	[redacted]
HR	heart rate
ICH	International Conference on Harmonization
ICF	informed consent form

IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
INR	international normalized ratio
[redacted]	[redacted]
[redacted]	[redacted]
kg	Kilogram
LDH	lactate dehydrogenase
L	Liter
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
[redacted]	[redacted]
NK	natural killer
NOAEL	no observed adverse effect level
[redacted]	[redacted]
OTC	over-the-counter
PBC	peripheral biliary cholangitis
PBL	peripheral blood lymphocyte
PD	Pharmacodynamics
PFT	pulmonary function test
PGA	Physicians Global Assessments
PI	Principal Investigator
PK	Pharmacokinetics
p.o.	per os (orally)
[redacted]	[redacted]
pSS	primary Sjögren's syndrome
PVG	Pharmacovigilance
q.d.	quaque die (once daily)
SAP	statistical analysis plan
S1P	sphingosine 1-phosphate
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
sec	Second
SOP(s)	standard operating procedure(s)
t1/2	elimination half-life
tmax	the median time to reach maximum plasma concentration

[redacted]	[redacted]
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VS	vital signs
[redacted]	[redacted]
WBC	white blood cell
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary

1. BACKGROUND

1.1. Background on Primary Biliary Cholangitis (PBC)

PBC is a rare, autoimmune, chronic, cholestatic liver disease, and is the most common cholangiopathy observed in adults [3]. It is characterized by a progressive bile duct injury from portal and periportal inflammation causing cholestasis, fibrosis, and eventually leading to liver cirrhosis. Although the precise cause of disease is unknown, there is evidence of liver immune infiltration and systemic aberrant immunity in PBC patients [2]. PBC affects individuals of all ethnic origins and accounts for 0.6%-2.0% of deaths from cirrhosis worldwide. Incidence rates for Europe, North America, and Australia range from 0.33 to 5.8 per 100,000 inhabitants and prevalence is 1.91 to 40.2 per 100,000 inhabitants, respectively. PBC disproportionately affects women (10:1 women to men ratio) [8,9].

The pathogenesis of PBC includes both adaptive and innate immune responses and evidence indicates that environmental, infectious, and genetic factors are involved [3]. Approximately 7-34% of patients with PBC have overlapping Sjögren's syndrome[10] and approximately 10% of patients with PBC have autoimmune hepatitis as well [11]. Chronic inflammation of the small interlobular bile ducts leads to cholangitis, ductopenia, and ductal proliferation [3]. These bile ductal injuries gradually progress to cholestasis, biliary fibrosis, and cirrhosis, which will eventually lead to liver failure if untreated. The risk of hepatocellular, colorectal and hepatobiliary cancers is also increased in patients with advanced stage PBC [12].

The diagnosis of PBC is based on a sustained elevation of serum markers of cholestasis (i.e., ALP), and the presence of serum AMA directed against the E2 subunit of the mitochondrial pyruvate dehydrogenase complex [10]. Other autoantibodies, such as ANA, are often identified in patients with PBC. The ANAs anti-Sp100 and anti-gp210 have a high specificity for PBC and could be helpful when AMA is negative [10].

Historically, PBC is characterized by florid bile duct lesions with injuries to biliary epithelial cells, an extensive portal inflammatory infiltrate, and progressive loss of small intrahepatic bile ducts [3]. The most frequent symptoms in PBC patients are fatigue and pruritus, occurring in nearly 80% and 20-70% of patients, respectively [10]. However, at the time of diagnosis, most patients are asymptomatic and are identified through the presence of abnormal liver enzymes during routine physical exams. Patients with PBC have a shorter survival than healthy subjects. In one follow-up study, the 10-year survival of PBC patients was 59%, compared with an expected 81% in the age- and sex-matched healthy population[13]. Patients with advanced PBC have a median survival of only 1.4-4.1 years [3].

1.1.1 Treatment Options

There is no cure for PBC. Liver transplantation is the only potentially curative treatment option for PBC patients. Furthermore, post-transplant recurrence of PBC is reported up to 34% [10,14]. The only pharmacological agents approved for the treatment of PBC are ursodeoxycholic acid (UDCA, 7β-epimer of the primary human bile acid chenodeoxycholic acid [CDCA], approved in the US in 1997) and obeticholic acid (OCA, approved in the US in 2016). Reports suggest that 10-20 mg/kg/day UDCA delays the need for transplantation or prolongs survival without liver transplantation; however, an estimated 40% of PBC patients are incomplete biochemical responders (reduction in ALP) to long-term UDCA monotherapy [10,15]. Reduction of ALP with UDCA has been recognized as a surrogate marker of slower disease progression and improved transplant-free overall survival [15]. PBC patients who do not

respond to UDCA continue to have significant symptoms and a high risk of developing serious complications.

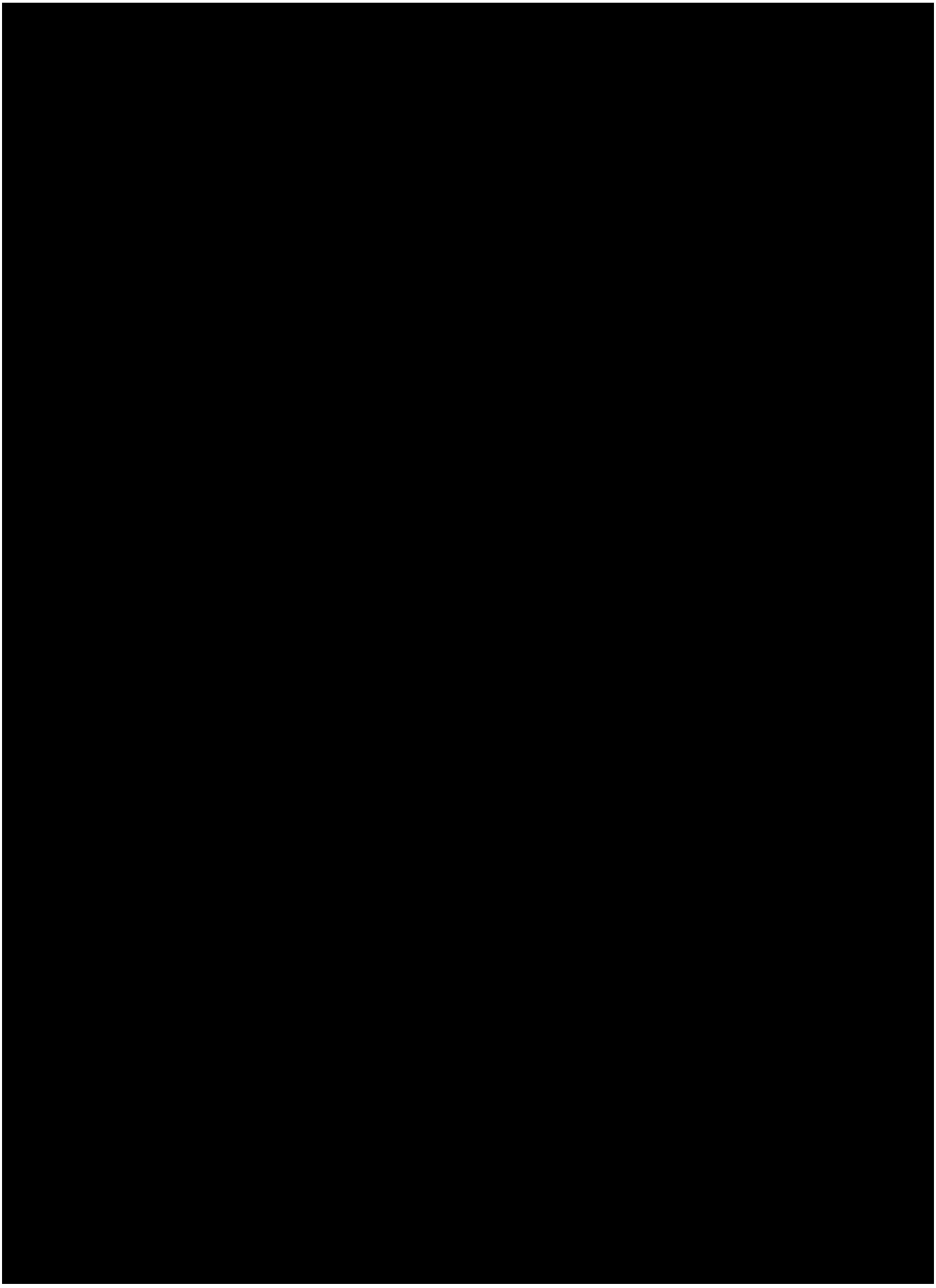
Various medications have been used as monotherapy or in combination with UDCA in patients unresponsive to UDCA. These include systemic corticosteroids, fibrates, antiproliferatives, immunosuppressants, colchicine and herbal medications [15]. However, the efficacy or long-term benefits of these medications are either negative or remain largely unknown.

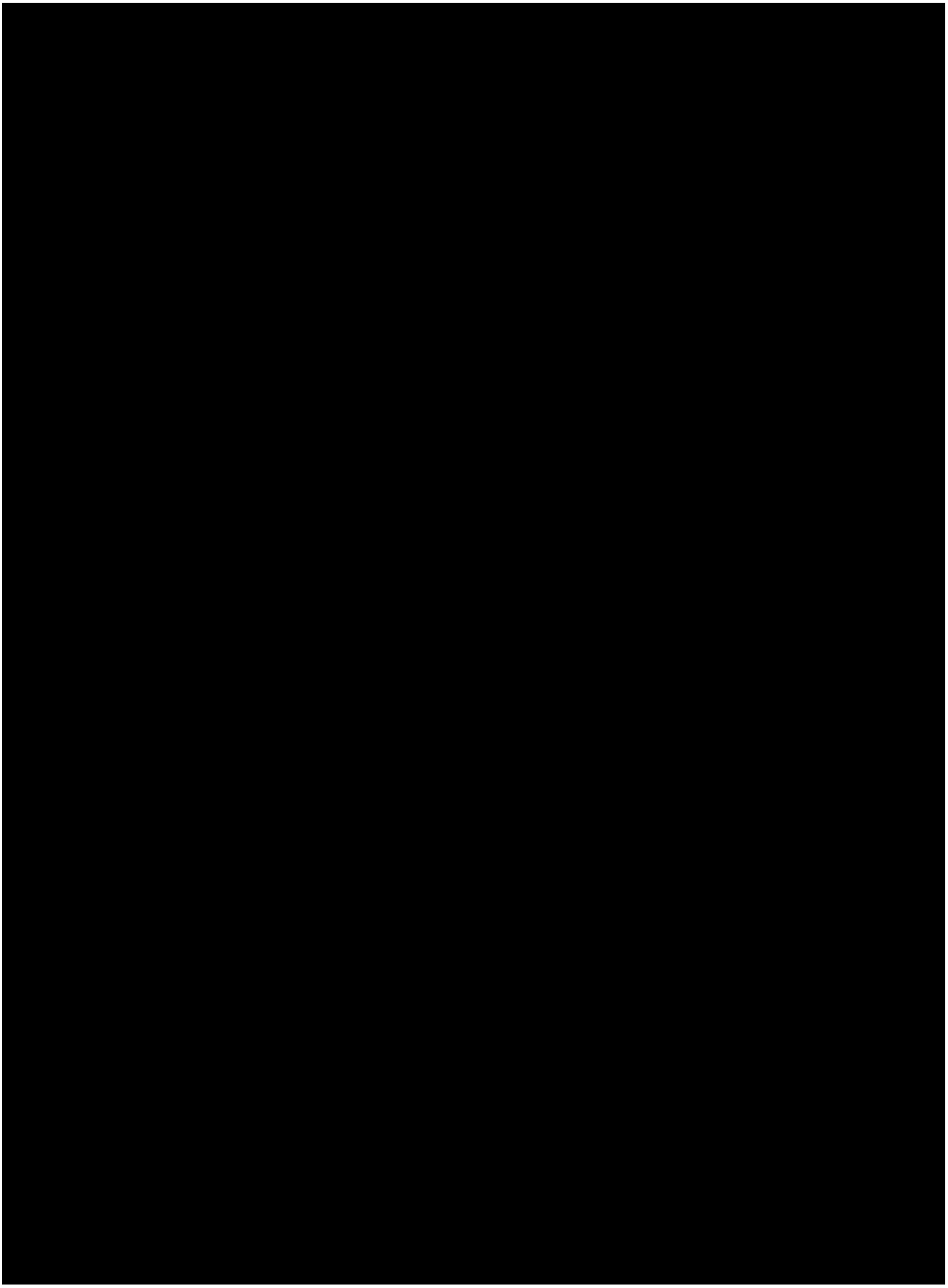
OCA is a novel derivative of the primary human bile acid CDCA, which is a potent farnesoid X receptor agonist. Reduction in ALP has been observed in up to 47% of patients treated with a combination of UDCA and OCA [16]. However, [redacted] Thus, although progression of disease is slowed for patients on UDCA and OCA, a safe, well tolerated, and effective medication needs to be developed. A significant unmet medical need still exists in patients who are unresponsive or intolerant of UDCA therapy.

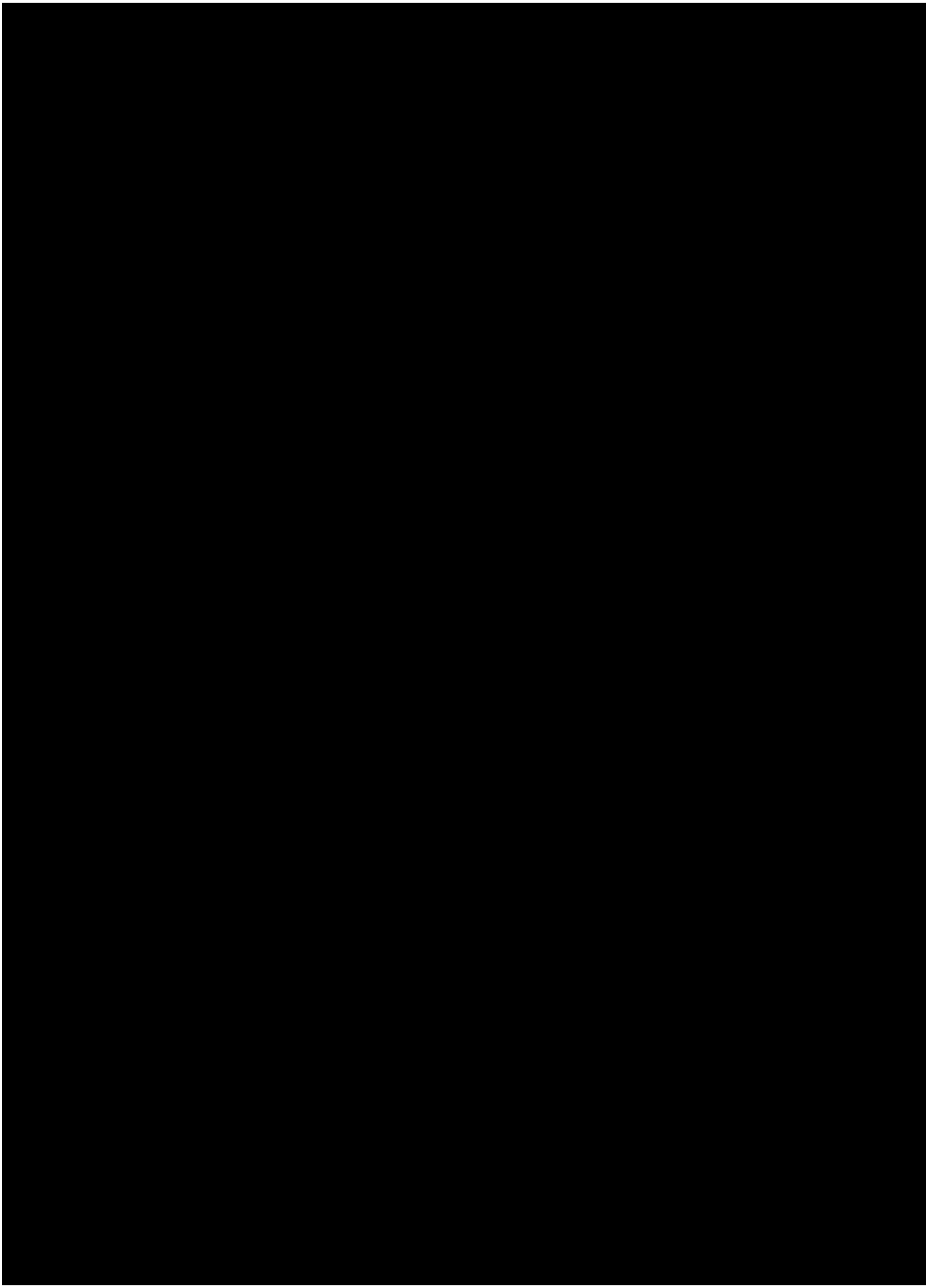
1.2. Background on Etrasimod

Etrasimod is an orally available, selective, S1P receptor modulator. S1P is a signaling sphingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient. The $S1P_1$ receptor is a physiological mediator that has been shown to regulate lymphocyte recirculation between lymphoid tissue and blood. Binding and internalization of the $S1P_1$ receptor may result in lymphocyte retention within lymphoid tissue, with subsequent reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation. $S1P_1$ receptor surface expression is required for S1P gradient-mediated lymphocyte migration out of lymphoid tissue into the circulation [1]. The preclinical and clinical data of etrasimod are summarized in the following sections.

[redacted]







1.3. Rationale for Treatment, Study Design and Dose Selection

1.3.1. Rationale for Treatment

S1P1 receptor signaling on certain lymphocyte subpopulations allows their exit from lymph nodes along a S1P gradient. Functional antagonism, through agonism and subsequent internalization, of these $S1P_1$ receptors results in retention of certain lymphocyte subpopulations in lymph nodes and prevents their egress to the bloodstream. It is through this mechanism that etrasimod may potentially reduce inflammation and autoimmune response in PBC. Lymphocyte lowering has been correlated with clinical efficacy for S1P functional antagonists in MS (fingolimod, ponesimod, siponimod, ozanimod)[25], psoriasis (ponesimod)[26] and ulcerative colitis (ozanimod) [27]. This same mechanism may also be useful in treating a variety of different inflammatory and autoimmune diseases. The availability of lymphocyte trafficking agents such as etrasimod would offer PBC patients an anti-inflammatory/autoimmune response, oral, and potentially more convenient treatment.

T cells are important players in the pathogenesis of PBC. The disease results from a chronic inflammatory process in which T cells attack the small bile duct epithelial cells. These epithelial cells eventually disappear, causing cholestasis and further progression of PBC. The T cells seem to be of both CD4+ and CD8+ origin, as shown by immunohistochemical staining in portal and periportal areas [2]. The trigger of this autoimmune disease is unknown, but genome-wide association studies have suggested the importance of certain HLA variants and other immune-related genes, such as components of the IL-12 signaling cascade. Furthermore, more than 95% of patients also develop a humoral autoimmune response to mitochondrial proteins [2,3].

The reduced peripheral lymphocyte availability seen with the $S1P_1$ modulator etrasimod is expected to decrease T cell recruitment to sites of inflammation, such as around the bile ducts. In addition to $S1P_1$ modulation, the receptor activity with $S1P_4$ and $S1P_5$ may confer additional immunomodulatory effects that could translate into efficacy for the treatment of PBC. NK cells appear to be involved in the pathogenesis of PBC: their levels increased in blood and liver of patients with strong cytotoxic activity against biliary epithelial cells [4], and resting as well as activated NK cells express $S1P_1$, $S1P_4$ and $S1P_5$ receptors. The $S1P_5$ receptor has been reported to be involved in chemotaxis of NK cells[5]. Other cells that may possibly be blocked by etrasimod include neutrophils, which are $S1P_4$ dependent [6].

In addition to immune cells, S1P receptors are expressed in hepatocytes, of which $S1P_1$ and $S1P_2$ appear most dominant. Inhibition of $S1P_1$, but not $S1P_2$ receptors, reduced bile salt (glycochenodeoxycholic acid)-induced apoptosis in rat hepatocytes, indicating potential therapeutic benefits in PBC [28]. Furthermore, it has been reported that $S1P_1$ may be involved in processes promoting liver fibrosis, suggesting that blockade of the $S1P_1$ pathway may help attenuate liver fibrosis [29].

Together, this evidence suggests that immune cells, in addition to hepatocytes, play a role in PBC and that $S1P_1$, and possibly $S1P_4$ and $S1P_5$, receptor modulation may represent a novel therapeutic approach in PBC.

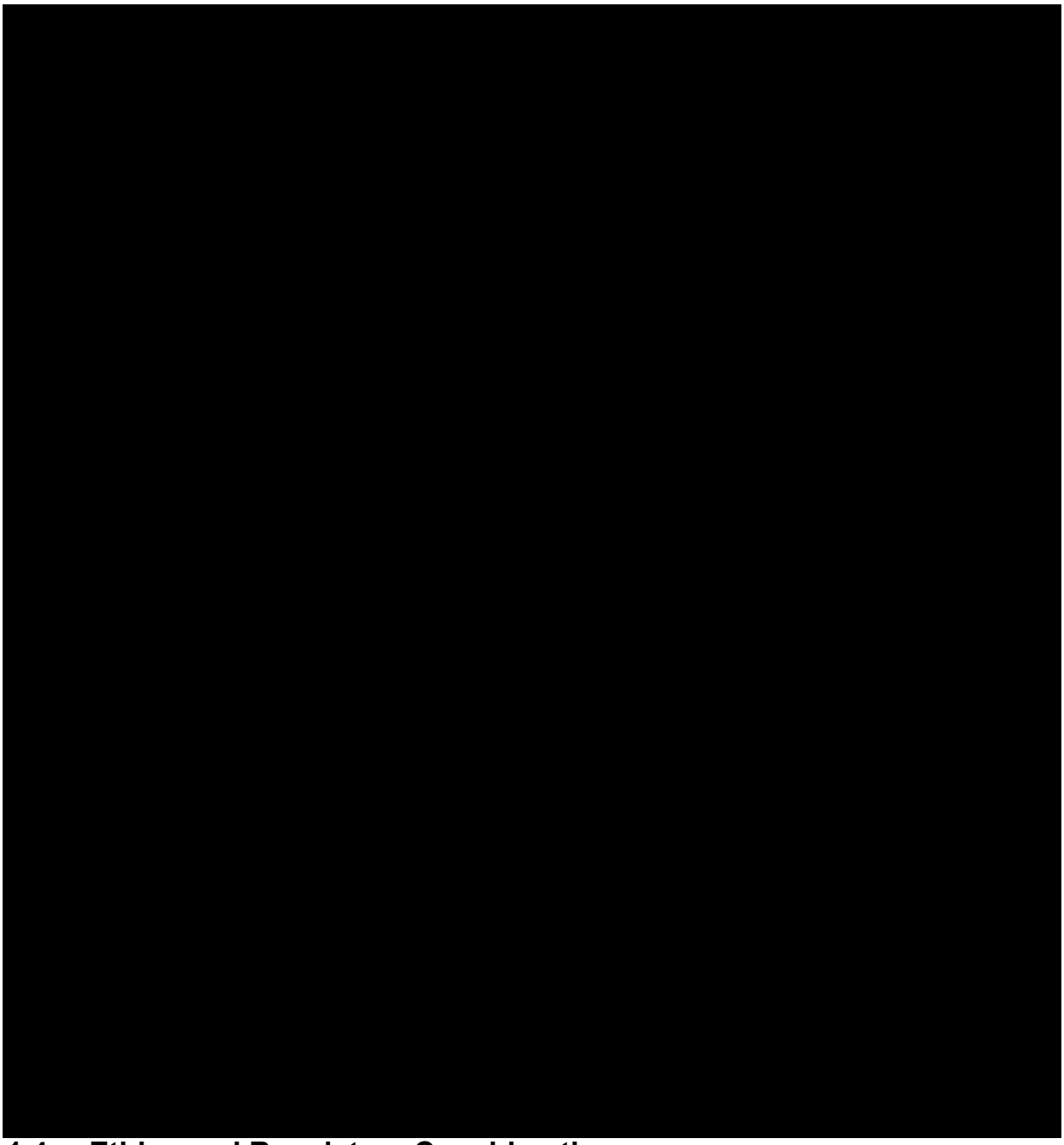
The aim of the proposed clinical study is to evaluate the role of S1P receptor modulation in the setting of PBC. Next generation S1P receptor modulators with improved side effect profiles, such as etrasimod, may represent a novel therapy for PBC patients.

1.3.2. Rationale for Study Design

This is an open-label, multicenter, dose escalation study to evaluate the safety, tolerability, PK and efficacy of two oral etrasimod daily doses (1 mg and 2 mg) for a total of 24 weeks (12 weeks at each dose level) in up to 20 patients with early stage PBC. In each patient, 1 mg daily will be evaluated initially for 12 weeks followed by a potential dose escalation to 2 mg daily based on each individual patients' safety and PK data. The open- label nature of the study allows for each subject to be evaluated closely for dose escalation based on their safety and PK data. The pharmacological activity and efficacy of etrasimod will also be evaluated. Clinically, PBC is monitored by assessing biochemical markers primarily, ALP levels, and other liver enzymes including gamma- glutamyltransferase (GGT) and bilirubin. Given the nature of these measures it is reasonable to plan an initial evaluation of clinical response without inclusion of placebo controls in this study.

A 3-month (12-week) treatment period for each dose level was chosen to assess the safety, efficacy and pharmacodynamic activity in patients. This timeframe is judged appropriate to establish an initial safety and clinical effect of etrasimod in PBC patients. Although this study is only including patients with early stage of PBC disease, it is possible that clearance of estrasimod may be decreased and systemic exposure increased. For this reason, the study was designed to assess the PK of the low dose (1 mg) after the initial dose on Day 1 and on Week 2 (i.e. steady-state) in each patient prior to allowing a dose escalation to 2 mg at Week 12.

1.3.3. Rationale for Dose Selection



1.4. Ethics and Regulatory Considerations

The study will be conducted in compliance with the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), applicable local regulatory requirements, the study protocol, and where applicable, sponsor and/or Contract Research Organization (CRO) Standard Operating Procedures (SOPs). The protocol and informed consent will be submitted for consideration by the appropriate IEC and written approval from the Chair or designated deputy of the IEC is required before clinical activities of the study can commence.

Any changes to the protocol will be made by means of a formal written protocol amendment. All amendments will require IEC approval before implementation except when changes to the protocol are required immediately to eliminate hazards to the volunteer/patient or when the changes involve only logistical or administrative aspects of the trial (for example, change of medical monitor, change in telephone number, etc.).

2. STUDY OBJECTIVES

2.1. Primary Objectives

Safety

- To assess the safety and tolerability of etrasimod in patients with PBC.

2.2. Secondary Objectives

Efficacy and PK

- To evaluate the efficacy (i.e., changes in ALP levels from baseline) of etrasimod in patients with PBC.
- To assess single dose and steady-state PK of etrasimod in patients with PBC.

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess the PD response (lymphocyte counts and subsets thereof).
- To assess serum hsCRP, ALT, AST, GGT, AMA, [redacted] C4, [redacted], total IgG and IgM.
- To assess QoL and incidence of pruritus and fatigue.
- [redacted].
- To assess changes in Schirmer [redacted] tests in patients with abnormal results at screening.

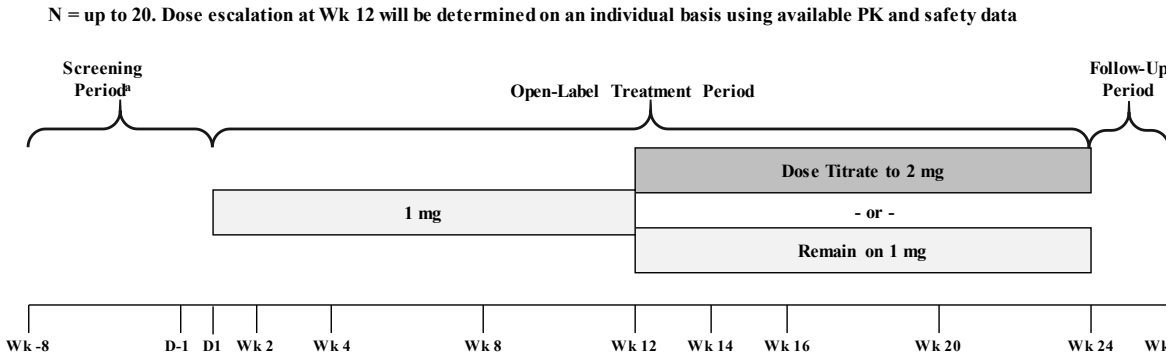
3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an open label, single arm, multi-center clinical study to assess the safety and tolerability, PK and efficacy of etrasimod in patients with PBC. The trial will include adult patients, 18-80 years of age, with a confirmed PBC diagnosis, and who had an inadequate response to UDCA.

The screening period will last 5 to 8 weeks and will be followed by a 24-week treatment period. All patients will receive 1 mg etrasimod for 12 weeks followed by a potential dose increase to 2 mg etrasimod for 12 weeks. Those patients who do not dose escalate will remain on 1 mg etrasimod for the duration of the study through Week 24 (Figure 1). During the treatment period, patients will need to take 1 tablet of study medication (p.o. q.d.). The last dose is planned to be taken one day before the end of the treatment period (during Week 24). A follow-up visit will take place 2 weeks after the end of treatment. Please refer to the Schedule of Procedures and Visits (Table 1) for the detailed plan.

Figure 1. Schematic of APD334-010 Study Design



[a] Screening Visit 1 is to occur between Week -8 and Week -5. Screening Visit 2 is to occur at least 4 weeks from Screening Visit 1. For patients with ALP, ALT, AST, or total bilirubin values from Screening Visits 1 and 2 that are not within 20% of each other (see Inclusion Criterion 9), an unscheduled visit within the screening period may be conducted to repeat these assessments.

The study will consist of the following periods:

Screening Period (5 to 8 weeks before baseline visit):

Each patient will be asked to visit the study site at least 2 times for screening assessments within the 8 weeks prior to the planned start of the treatment (Day 1). Screening Visit 1 is to occur between Week -8 and Week -5. Screening Visit 2 is to occur at least 4 weeks from Screening Visit 1. For patients with ALP, ALT, AST, or total bilirubin values from Screening Visits 1 and 2 that are not within 20% of each other (see Inclusion Criterion 9), an unscheduled visit within the screening period may be conducted to repeat these assessments.

All patients must be consented before any study specific procedure is performed and written informed consent must be obtained. Patients will then undergo screening procedures to determine eligibility.

[redacted]

Treatment Period (24 weeks):

The study will assess safety, tolerability, PK and efficacy of etrasimod in up to 20 eligible patients. Patients will come to the clinic [redacted]. Vital signs and ECG changes will be monitored extensively during this time, and PK sampling will be performed (6.13). Patients will receive a 1 mg etrasimod tablet (p.o., q.d.) from Day 1 onwards. If the 1 mg dose is well tolerated and there are no clinically significant changes in vital signs and ECG, the 1 mg dose level will be maintained. If 1 mg is not tolerated, then treatment will be stopped per the dose-stopping rules (5.2.1). The 1 mg dose level may be increased to 2 mg at week 12, based on the patient's safety and PK data. This data will be reviewed by a safety and dose escalation committee who will decide whether to proceed with dose escalation. Patients with dose escalation on Week 12 will have PK sampling [redacted] (6.13), and vital signs and ECG monitoring performed [redacted]

Visits [redacted]: Patients will return to the study site and all planned examinations as described in Schedule of Procedures and Visits (Table 1) will be conducted. [redacted] only dose escalated patients will visit. Last dose of study medication is planned 1 day before the end of the treatment visit at Week 24.

Follow up Visit/End of Study Visit:

Visit [redacted] *after end of treatment:* Patients will return to the study site for the final visit, and final procedures will be performed per Schedule of Procedures and Visits (Table 1).

Premature Discontinuation: All procedures planned for Weeks 24 and 26 visits should be performed for all patients who discontinue the study prematurely.

3.2. Study Duration

The study duration will be up to 34 weeks per patient, with 5 to 8 weeks for screening, followed by a 24-week treatment period (including a 12-week 1 mg treatment period followed by a 12-week 2 mg treatment period if tolerable) and a follow-up visit 2 weeks after the end of treatment.

The Schedule of Procedures and Visits for the study is provided in Table 1.

3.3. End of Study

The EOS is defined as the last patient last visit in the follow-up period, or earlier, if one of the following is documented for all treated patients: withdrawal from the study, loss to follow-up, death, or the study is prematurely terminated by the sponsor, whichever occurs first.

[redacted]

[redacted]

4. STUDY POPULATION

The study population will consist of up to twenty (20) PBC patients without cirrhosis who fulfill eligibility (inclusion & exclusion) criteria.

4.1. Inclusion and Exclusion Criteria

Each patient must meet the inclusion and exclusion criteria described below to be enrolled in the study. Inclusion and exclusion criteria that refer to an assessment being performed "at screening" are referring to Screening Visit 1 unless specified otherwise.

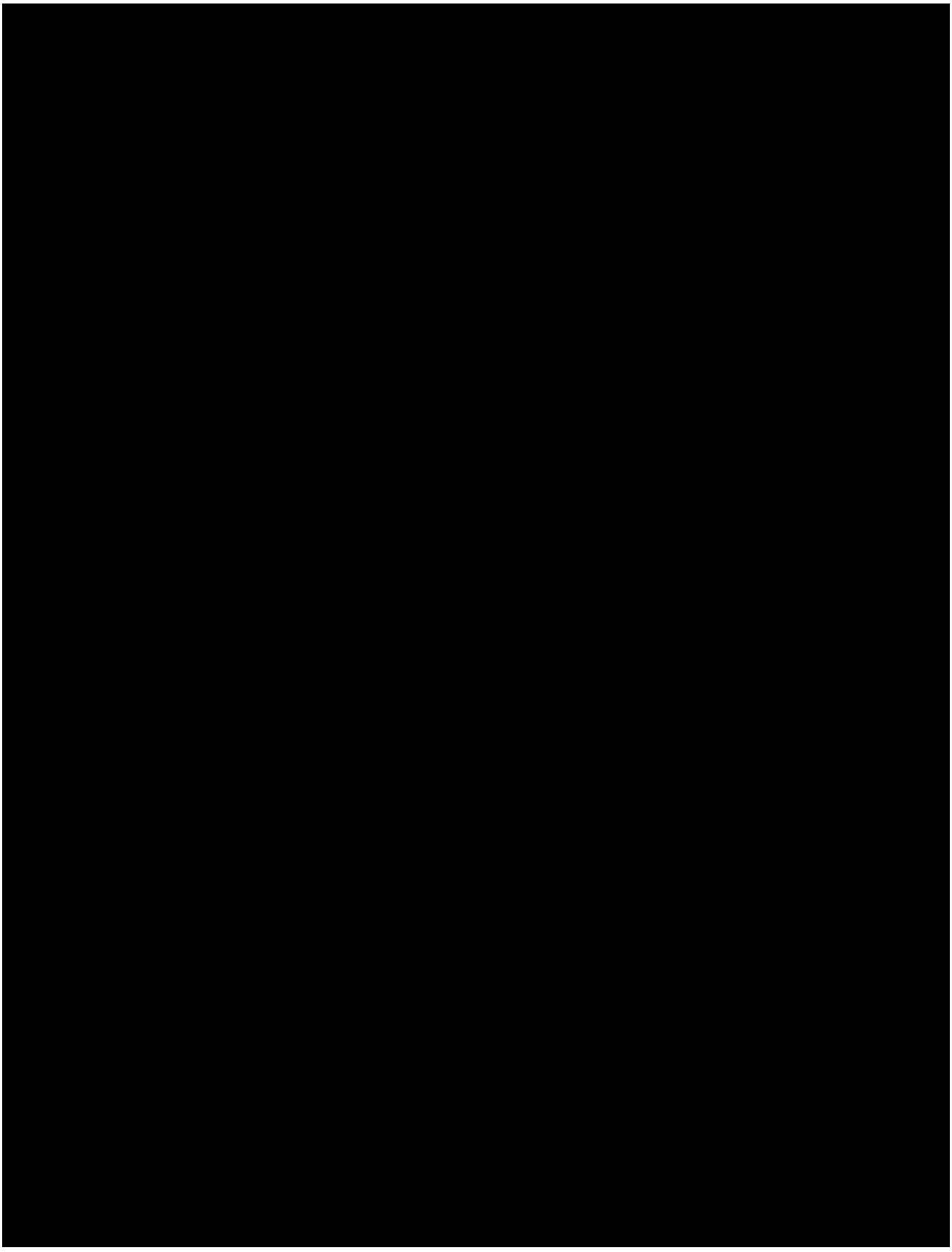
4.1.1. Inclusion Criteria

1. Males or females aged 18 to 80 years (inclusive) at the time of screening, with confirmed PBC diagnosis based upon at least 2 of 3 criteria:
   - AMA titer >1:40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies (anti-GP210 and/or anti-SP100)
   - ALP >1.5 × ULN for at least 6 months
   - Liver biopsy findings consistent with PBC
2. Use of UDCA for at least 6 months prior to screening (stable dose for at least 3 months immediately prior to screening)

[redacted]

4. Patients must have the following laboratory parameters at screening
   - ALP >1.5 × ULN but <10 × ULN (at all screening visits)
   - ALT and AST <5 × ULN (at all screening visits)
   - Total bilirubin <ULN (at all screening visits)

[redacted]



[redacted]

8. AST, ALT, ALP, and total bilirubin must have 2 values at least 4 weeks apart that are within 20% of each other.

4.1.2. Exclusion Criteria

1. Chronic liver disease of a non-PBC etiology. However, PBC patients accompanied with pSS are eligible to be enrolled.
2. History or evidence of clinically significant hepatic decompensation:

[redacted]

3. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease).

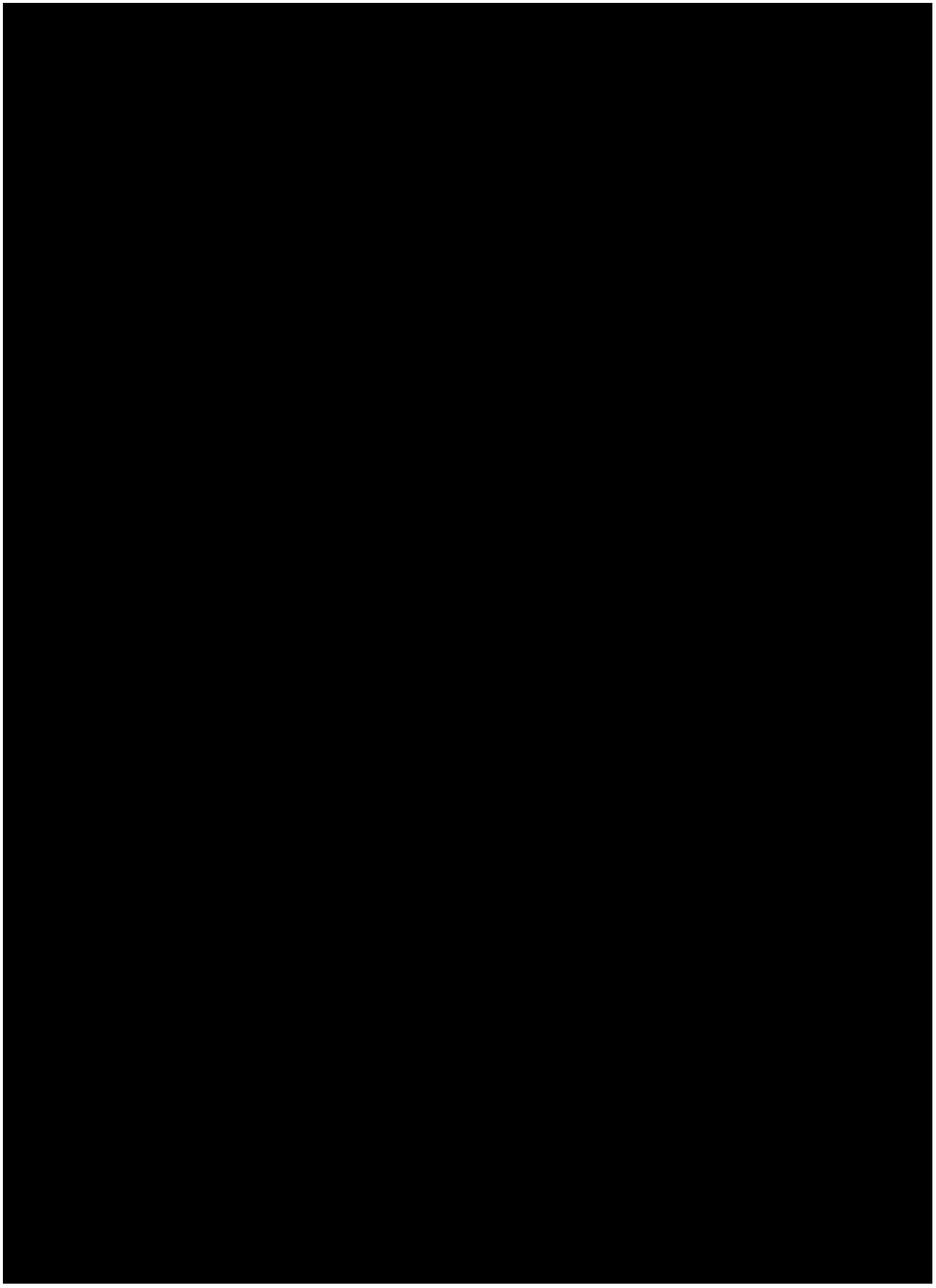
[redacted]

7. Infection with hepatitis C virus anytime in the past; confirmed active infection with hepatitis B virus at screening.

[redacted]

13. Treatment with OCA within 30 days prior to Day 1.
14. Other immunosuppressive, immunomodulating or antineoplastic agents not listed in Permitted Medications section below within 30 days prior to Day 1 (or not meeting the stability time period for concomitant medications indicated as permitted).

[redacted]



5. STUDY TREATMENT(S)

5.1. Study Drug

Etrasimod is an investigational product and will be provided by the sponsor for the study. Etrasimod will be supplied as 1 mg and 2 mg immediate release tablets, packaged in high-density polyethylene bottles with child-resistant screw caps. [redacted]

5.2. Dosage, Administration and Accountability

Investigational product will be dispensed to the patients under the supervision of the investigator or his/her designee; 1 mg or 2 mg tablet p.o., based on available PK and safety data (vital signs and ECG). [redacted]

Investigational product will be dispensed as follows:

- [redacted] The responsible investigator or designee at clinic will dispense tablets as appropriate. Patient will return the bottle with all remaining tablets [redacted].
- [redacted] Patient will return the bottle with all remaining tablets [redacted].
- [redacted] Patient will return the bottle with all remaining tablets [redacted].
- [redacted] Patient will return the bottle with all remaining tablets [redacted].
- [redacted] Patient will return the bottle with all remaining tablets [redacted].
- [redacted] Patient will return the bottle with all remaining tablets [redacted].
- [redacted] Patient will return the bottle with all remaining tablets [redacted].

The investigator will maintain accurate records of the receipt of all study medication. In addition, accurate records will be kept regarding when and how much study medication is dispensed and used by each patient in the study.

Investigational product accountability will be performed by the site [redacted]

Reasons for deviation from the expected dispensing regimen must also be recorded. Study medication will be reconciled by the sponsor's monitor or contracted designee. The investigator agrees to provide sufficient access to study medication as required for the reconciliation process to be completed in a timely fashion.

5.2.1. Dose-stopping Rules

Any of the following findings in a patient during treatment will lead to a stop in etrasimod dosing in the affected patient:

- Certain ECG changes (see details 6.6), **or**
- Clinical evidence of drug-induced liver injury (DILI; as described in 6.15)

As described in 3.1, at the discretion of the PI, the dose of etrasimod may be adjusted from 2 mg q.d. back to 1 mg q.d. if deemed necessary. If the patient is on 1 mg, the PI may discontinue etrasimod treatment if deemed necessary based on the dose-stopping rules.

5.3. Investigational Product Retention at Study Site

At completion of the study, all study medication will be reconciled by the sponsor's monitor or contracted designee, and then returned at the direction of the sponsor to be retained or destroyed per applicable country regulations. Prior to any action being taken with study medication after the study is completed, the investigator will contact the sponsor (or contracted CRO) for approval of such action.

5.4. Study Restrictions

[redacted]

5.5. Safety and Dose Escalation Review Committee

A safety and dose escalation review committee will be established to review PK and safety data from the PBC patients, and guide dose escalation in order to maintain patient safety. The committee will make recommendations on whether to proceed with the 2 mg dose at Week 12 based on acceptable PK [redacted] and available safety data (including ECG changes) [redacted].

6. STUDY PROCEDURES

6.1. Informed Consent

Prior to undergoing any study specific procedures, each subject must sign a written Informed Consent Form (ICF) that has been approved by the investigator's designated Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and by the sponsor. All patients will be informed of the nature of the protocol and investigational therapy, their possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The signed ICF should be included in the patient's medical record, which should also contain written documentation indicating that informed consent was obtained. Study procedures will be conducted only after a written informed consent has been obtained and documented appropriately in the source data.

6.2. Screening Failures

A screening failure is defined as a patient who has signed the ICF, does not meet all the entry criteria as outlined in this protocol and has not been randomized or received study medication. A screening log will be maintained by the Investigator or designee, indicating the reason for the screening failure.

6.3. Medical History

A complete medical history will be collected at screening. Concomitant medications, recent illnesses, and participation in other investigational drug studies will also be recorded. The examinations will be performed as outlined in Schedule of Procedures and Visits (Table 1).

6.4. Physical, [redacted] and Neurological Examinations

6.4.1. Physical Examination

The examinations will be performed as outlined in Schedule of Procedures and Visits (Table 1). The physical examination will be performed by the investigator. It will include assessments of general appearance, skin, head (eyes, ears, nose, and throat), neck, thyroid, lungs, heart, abdomen, back, lymph nodes, and extremities, and body weight. Height will only be obtained at screening. Patients with eye disturbances indicating macular edema, such as blurred vision in combination with metamorphopsia, must be referred to an ophthalmologist for further examination.

[redacted]

6.4.3. Neurological Examination

The neurological examination includes assessments of the neurological system (cranial nerves, motor and sensory function, coordination, and mental status). In addition, monitoring for PML will be performed [redacted] using a subjective PML checklist (refer

[redacted] The examinations will be performed as outlined in Schedule of Procedures and Visits (Table 1).

6.5. Vital Signs

Supine (laying face upward) blood pressure, heart rate, temperature, and respiratory rate will be measured after the patient has been resting for 5 minutes. Vitals signs will be measured prior to any blood draw or any other invasive procedure that occurs at the same visit or time point. Vital signs will be measured according to the time points in the Schedule of Procedures and Visits (Table 1). Vital signs are to be measured [redacted] of the scheduled timepoint.

6.6. Electrocardiography

6.6.1. ECG Equipment

Safety ECGs will be recorded from an ECG machine (12-lead). Safety ECGs will be printed and reviewed on-site by the PI or other physician (e.g., cardiologist). Typically, all safety ECGs will be obtained as single tracings, with the exception of the pretreatment ECG obtained on Day 1, which is a triplicate recording.

6.6.2. ECG Acquisition

The safety ECG equipment will be set according to ECG and [redacted].

6.6.3. ECG Assessment

Safety ECGs will be performed as outlined in Schedule of Procedures and Visits (Table 1). ECGs are to be measured [redacted] of the scheduled timepoint.

The PI or designee (physician) will be responsible for review and interpretation of safety ECG on-site and determining if the ECG is normal, abnormal “not clinically significant” or abnormal “clinically significant”. Abnormalities of particular interest include increased PR and QTc intervals, either absolute prolongations or clinically noteworthy increases from baseline values.

[redacted]

[redacted]

6.9. Clinical Laboratory Tests

The clinical laboratory tests will be performed as outlined in Schedule of Procedures and Visits (Table 1). Tests will be performed in the central laboratory. If the patient lives in a remote area, laboratory testing for close observation for possible DILI may be performed locally and the results promptly communicated to the clinic.

In the event of abnormal clinical laboratory values, the physician will make a judgment whether or not the abnormality is clinically significant. If clinically significant, it will be captured and recorded as an AE.

6.9.1. List of Laboratory Parameters

Laboratory tests will include the following:

Serum Chemistry

Albumin (ALB)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT; SGPT)
Amylase
Aspartate aminotransferase (AST; SGOT)
Bicarbonate
Blood urea nitrogen (BUN)
Calcium (Ca)
Chloride (Cl)
Creatinine
Creatine kinase and MB subtype (if elevated) (% and total MB)*
Gamma-glutamyl transferase (GGT)
Glucose
Lactate dehydrogenase (LDH)
Lipase
Magnesium
Phosphate
Potassium (K)
Sodium (Na)
Total bilirubin
Direct bilirubin
Total protein

Serum Chemistry Lipid Panel

High-density-lipoprotein (HDL)
Low-density-lipoprotein (LDL)
Total cholesterol (TC)
Triglycerides (TG)

Hematology

Hematocrit (Hct)
Hemoglobin (Hb)
Lymphocyte subsets (CD4, CD8 and NK cells)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular volume (MCV)
Platelet count
Red blood cell count (RBC)
White blood cell count (WBC) with differential (% and absolute counts)

Coagulation

Prothrombin time (PT)
Activated partial thromboplastin time (PTT)
International Normalized Ratio (INR)

Additional tests

[redacted]
Urine dipstick test
Follicle stimulating hormone (FSH)
[redacted]
AMA
[redacted]

Additional tests at screening

[redacted]
HBsAg
Anti-HCV
[redacted]
QuantiFERON
Thyroid-stimulating hormone (TSH)
Triiodothyronine (free T3)
Thyroxine (free T4)

* alternatively, this can be done by troponin test (T and or I)

[redacted]

6.9.3. Urinalysis

Urinalysis will follow the local practice at the study site (as dipstick). Tests will be performed as outlined in Schedule of Procedures and Visits (Table 1). Parameters for clinical laboratory tests include the following:

- appearance + color
- specific gravity
- pH
- leukocytes
- protein
- glucose
- nitrites
- ketones
- urobilinogen
- bilirubin
- blood/erythrocytes

Microscopic urinalysis will be performed when there is a positive or abnormal macroscopic urinalysis result as deemed necessary by the investigator.

6.9.4. Sample Collection

All blood and urine samples will be collected according to site standards. Tests will be performed as outlined in Schedule of Procedures and Visits (Table 1).

6.9.5. Blood Volume

The total blood volume collected from each patient participating in the study (according to the sampling described in the Schedule of Procedures and Visits [Table 1]) is estimated to be 340 mL, but will not exceed 500 mL.

[redacted]

6.11.1. Patient 5-D Pruritus Scale

The patient 5-D itch scale was developed as a brief but multidimensional questionnaire designed for pruritus and to be useful as an outcome measure in clinical trials as it measures changes over time. The five dimensions are degree, duration, direction, disability and distribution. This assessment sheet will be completed by the patient as per Schedule of Procedures and Visits (Table 1).

6.11.2. Patient PBC-40 Quality of Life Scale

The PBC-40 is a disease specific health related quality of life measure for PBC, scored on a scale of 1 to 5 (where 1 = least impact, 5 = greatest impact) grouped into six domains (symptoms, itch, fatigue, cognition, social, and emotional). For each domain, scoring involved summing individual question response scores. Higher scores indicate a poorer quality of life. This assessment sheet will be completed by the patient as per Schedule of Procedures and Visits (Table 1).

6.12. Hematologic Assessments

6.12.1. Complete Blood Count

Blood samples for CBC with differential and platelet count, as well as lymphocyte subsets, will be assessed. Tests will be performed as outlined in Schedule of Procedures and Visits (Table 1).

If the absolute peripheral lymphocyte count has not recovered to at least 80% of the baseline value, or within normal ranges, at the 2-week follow-up (week 26), the patient must return for weekly CBCs until the absolute peripheral lymphocyte count has returned to at least these values.

6.13. Pharmacokinetic Assessments

Patients will have a serial PK sampling [redacted]

[redacted] All PK samples are to be collected [redacted] of the scheduled timepoint.

PK data [redacted] will support the dose escalation of etrasimod in PBC patients at Week 12. An additional PK blood sample will be collected, if possible, at the time of any intolerable AE (an AE leading to study drug discontinuation) or SAE. Sampling will be performed as outlined in Schedule of Procedures and Visits (Table 1).

At each PK time point, approximately 2 mL of blood will be collected, and the plasma will be harvested. Plasma samples will be shipped to the analytical lab for analysis of etrasimod and its putative metabolites (if possible). After the completion of study, samples will be transferred to sponsor designated storage site in US, and retained for future exploratory research related to the study drug. In general, the storage time is no more than 3 years. A PK sample collection manual will be provided to instruct the type of anticoagulant, the material supplies, sample processing, storage and shipping procedures.

6.14. C4 and [redacted]

C4 and [redacted] may be analyzed, if deemed necessary by the Sponsor, depending on ALP levels throughout the course of the study for exploratory objectives. For this purpose, back up PK samples will be used.

6.15. Adverse Events Assessments

Patients will be monitored from ICF signature to 30 days after the last dose of study drug for AEs to the study drug and/or procedures.

AEs will be recorded and reported in accordance with ICH GCP. The definitions of AEs and serious AEs (SAEs) will be as given in ICH Guideline E2A, "*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*." The outcome of an AE will be defined according to ICH Guideline E2B(R3), "*Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*." The relationship to investigational product will be classified using World Health Organization (WHO) criteria.

6.15.1. Adverse Event Reporting

Patients will be instructed to report all AEs, which can be reported at any time. AEs that occur from ICF signature until the time of administration of the first dose of etrasimod will be regarded as 'pre-treatment' and recorded as an AE. All events reported following study medication administration up to 30 days after the last medication intake will be presented as treatment emergent AEs (TEAEs).

Monitoring of ongoing AEs will be continued up to 30 days after study medication administration.

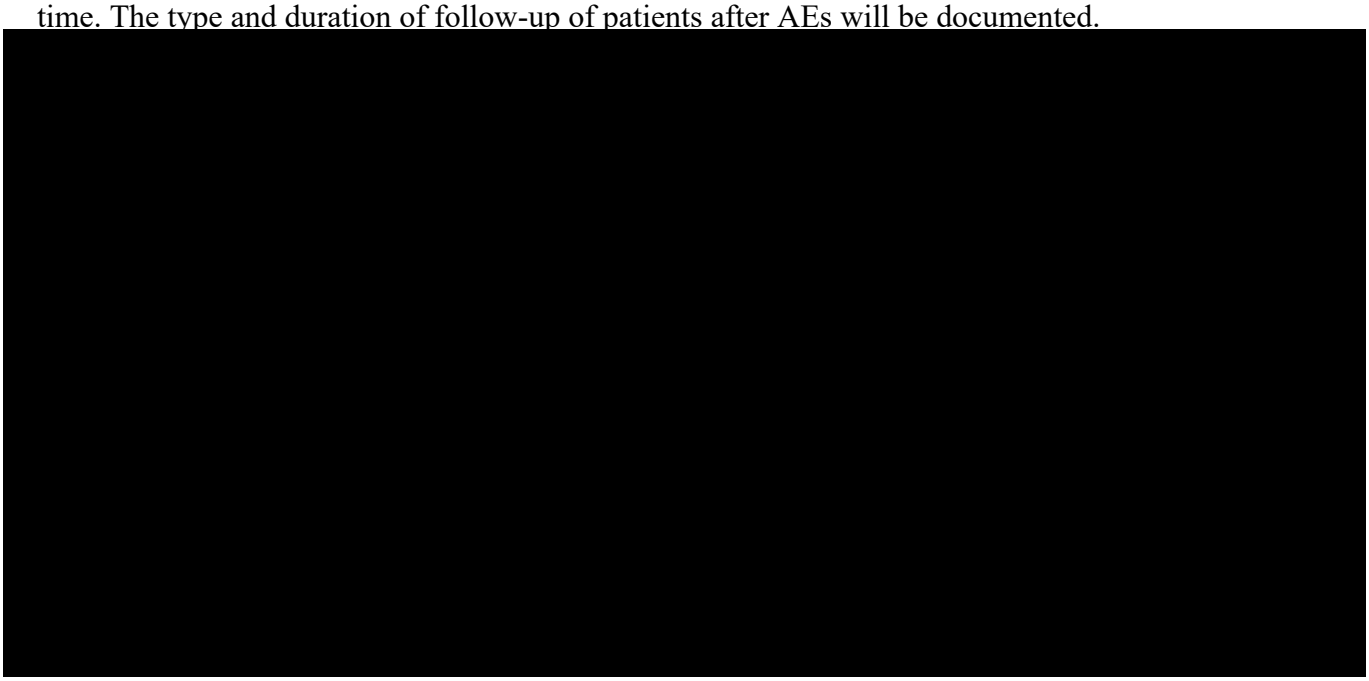
For this study, an AE is defined as: "Any untoward medical occurrence in a study patient administered etrasimod which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of the study medication, whether or not related to the product. AEs can be any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters observed in a patient in the course of a clinical study
- Pre-existing conditions which worsen in severity or frequency or which have new signs/symptoms associated with them

Lymphopenia will not be captured as an AE because it is an expected pharmacologic effect of the drug.

AEs will be elicited at the time indicated in the schedule. Any adverse or unexpected events, signs and symptoms will be fully recorded on the AE Form including details of intensity, onset, duration, outcome and relationship to the drug as determined by the PI. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self-limited fever, runny nose, cough, and scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). AEs may also be reported at any time. The type and duration of follow-up of patients after AEs will be documented.



6.15.2. Serious Adverse Events and Expedited Reporting of Adverse Events

An SAE is any untoward medical occurrence that at any dose results in the following outcomes:

- Death
- Is life-threatening
- Required/Prolonged hospitalization
- Disability/Incapacity
- Congenital anomaly/birth defect

- Important medical event

SAEs will be captured from the time of ICF signature to 30 days after the last dose of study drug, and will be monitored until resolution or stabilization.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such a medical event includes allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Elective hospitalization and/or surgery for clearly pre-existing conditions (for example a surgery that has been scheduled prior to the patient's entry into the study) will not be reported as a SAE. All other hospitalizations, including elective hospitalizations for any condition that was not pre-existing, will be reported as a SAE.

Any AE considered serious by the investigator or which meets SAE criteria must be reported to PPD Pharmacovigilance (PVG) within 24 hours from the time study site personnel first learn about the event.

The following contact information is to be used for SAE reporting:

EMEA ASIA Safety Central Mailbox: [redacted]
Australia: [redacted] (tel)
Australia: [redacted] (fax)

Or alternatively:

PPD Medical Affairs/Pharmacovigilance
PPD PVG Hotline: (United Kingdom number) [redacted] PPD PVG
Fax line: (United Kingdom number) [redacted]

A full description of every SAE will need to be provided to PPD PVG (this may be supported by source documentation such as laboratory reports or a discharge summary should the patient be hospitalized).

Other safety issues as defined in ICH Guideline E2A, and EU Eudralex Volume 10 also qualify for expedited reporting. In these situations, the process will be as detailed for SAEs above:

- SAEs which could be associated with the trial procedures;
- SAEs and AEs of special interest that could materially influence the benefit-risk assessment of a medicinal product, such as: a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the investigator brochure.

6.15.2.1. Patient and Patient-Partner Pregnancy

Patients who become pregnant during the study will be discontinued immediately. Although not considered an SAE or AE, pregnancies occurring during the period of study drug administration

(Day 1 to Week 24) until 30 days after the last dose of study drug should be reported to the sponsor contact and IEC in the same manner as an SAE.

Pregnancies will be followed every trimester through the first well baby visit. For female partners whom become pregnant by male study patients during the course of the study, reasonable efforts will be made to collect information on the partner's pregnancy through the first well baby visit as provided by the male study patient.

6.15.3. Assessment of Adverse Event Severity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of the AE will be graded according to the CTCAE v4.03 [31] definitions, listed below:

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 (ADL)*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Activities of Daily Living:

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.15.4. Assessment of Adverse Event Relationship to Study Medication

The relationship of an AE to investigational product(s) will be classified using modified WHO criteria (Edwards and Biriell, WHO Collaborating Centre for International Drug Monitoring 1994) as follows:

Related: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. Re-challenge information is not required to fulfill this definition; or an event that could also be explained by concurrent disease or other drugs or chemicals where information on drug withdrawal may be lacking or unclear.

Not related: a clinical event, including laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; proof of other cause; etc.); or an event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

6.15.5. Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to ICH Guideline E2B.

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Not recovered/not resolved
- Fatal
- Unknown

6.15.6. Action Taken for Adverse Event

Action taken for AEs will be documented according to the following:

- Concomitant medication or other treatment
- Withdrawal from the study

6.15.7. Action Taken for Study Drug

Any action taken with study drug will be defined according to ICH Guideline E2B and documented in the CRF according to the following:

- Drug withdrawn
- None (not changed)
- Dose interrupted
- Unknown
- Not applicable

6.15.8. Follow-up of Adverse Events Present at Last Scheduled Study Visit

Adverse events present at the last study day (Week 26/Exit) that require follow-up or a repeat laboratory test will be followed up initially for 30 days according to the site's standard practice for AE follow-up. AEs that have not resolved or stabilized at 30 days after the last patient's last study dose, will be reviewed with the sponsor on an individual basis to determine whether the database will be locked and subsequently updated once the events of ongoing AEs are resolved or whether database lock will be held.

6.16. Drug-Induced Liver Injury (DILI) Surveillance

In July 2009, the FDA released a Guidance for Industry entitled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," which reviews the importance of DILI surveillance in drug development. DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years, and hepatotoxicity discovered after approval for marketing has limited the use of many drugs. Furthermore, the guidance addresses how laboratory measurements that signal the potential for DILI can be obtained and evaluated during drug development.

Given the fact that all subjects enrolled in this study have pre-existing liver disease (i.e., PBC) and baseline elevations in laboratory tests of liver health (ALP, ALT and/or AST), DILI

surveillance is of critical importance to patient safety. Therefore, in collaboration with the FDA and after careful consideration of the principles outlined in the DILI guidance, the sponsor has established procedures to ensure early detection of possible DILI and study drug discontinuation in the context of suspected DILI.

6.16.1. Close Observation for Possible DILI

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. Close observation is mandatory for any study patient who meets one or more of the following "possible DILI" laboratory criteria:

- ALT or AST that is <ULN at baseline, followed by ALT or AST increase to >3 × ULN
- ALT or AST that is >ULN at baseline, followed by ALT or AST increase to >2 × baseline
- ALP >2 × baseline
- Total bilirubin >1.5 × ULN

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests within 48-72 hours. Then, repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities resolve, abnormalities stabilize, or the study drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering consultations, imaging studies, and/or therapeutic interventions, as required.

6.16.2. Study Drug Discontinuation for Suspected DILI

Should any patient who meets "possible DILI" laboratory criteria have persistence or worsening of lab data (i.e., ALT, AST, ALP, and/or total bilirubin) after one week of close observation, study drug must be discontinued. In addition, immediate study drug discontinuation is mandatory for any study patient who meets one or more of the following "suspected DILI" clinical criteria:

- ALT or AST <2 × ULN at baseline, followed by ALT or AST increase to >5 × baseline
- ALT or AST ≥2 × ULN but <5 × ULN at baseline, followed by ALT or AST increase to >3 × baseline
- ALT or AST increase to >2 × baseline AND concomitant total bilirubin increase to >2 × baseline
- ALT or AST increase to >2 × baseline AND concomitant INR increase >0.2
- Clinical signs and symptoms of liver inflammation, including but not limited to fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, jaundice, icterus, and/or eosinophilia (>5%)

6.17. Concomitant Medications and Procedures

All medications (over the counter [OTC] and prescribed) that are taken by patients and all procedures that are performed during the screening period and during the study must be recorded in the electronic case report form (eCRF) with start date/time and stop date/time, if known.

The following should be taken into account with regard to concomitant procedures:

- Patients may not undergo major elective surgery while enrolled in this study.
- Patients may not donate sperm, or oocytes during the study and for 30 days after the last dose of study drug.

6.17.1. Permitted Medications for the Treatment of PBC

UDCA should be at a stable dose for at least 3 months prior to screening and continue at pre-study dosing through the study period.

Medications (such as for pruritus and fatigue) used as adjunctive therapy for PBC in combination with UDCA should be at stable doses within 30 days prior to Day 1. These medications may be adjusted during study treatment but all adjustments must be recorded in the concomitant medications source documents and eCRFs.

6.17.2. Excluded Medications

The following medications are excluded prior or during the study:

- Drugs not allowed per the UDCA prescribing information [redacted]
- Fibrates (including bezafibrate) within 30 days prior to Day 1 and during the study.
- Treatment with OCA within 30 days prior to Day 1 and during the study.
- Immunosuppressive, immunomodulating agents [redacted]

- Investigational agents, other than etrasimod from 30 days prior to Day 1 and during the study.

6.18. Removal of Patients from the Trial or Study Drug

The study may be terminated early if, in the opinion of the sponsor, investigator, or IEC, an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of review of the key safety data. Evidence of macular edema in patients requires study drug discontinuation.

Patients will be free to withdraw from the study at any time should they so wish. A patient may be withdrawn from the study for any of the following reasons (including but not limited to):

- Clinical investigator may remove a patient if, in his/her opinion, it is in the best interest of the patient (including decisions based on the dose-stopping rules).
- Withdrawal of consent: Any patient may withdraw his/her consent from the study at any time. The investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.
- Deviation/noncompliance with the protocol or study drug.
- An AE.
- Lost to follow up.

6.18.1. Handling of Withdrawals

Although a patient is not obliged to give his/her reason for withdrawing prematurely, the investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a patient is prematurely discontinued from this study, every attempt will be made to follow the Week 24/EOS visit procedures. If consented by the patient, effort will be made to conduct a follow-up visit within 2 weeks of discontinuation (Table 1), if the patient has received at least 1 dose of the study drug.

6.18.2. Replacements

Patients who terminate early from the study due to reasons other than AEs will be replaced.

6.19. Study and Site Discontinuation

The sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

Additionally, if more than three patients develop a CTCAE Grade 3 or higher event in the same category, or if three or more patients meet one of the individual stopping rules, the safety and dose escalation review committee (5.5) will convene to evaluate the findings. Further, dosing will be stopped in randomized patients and no new patients will be randomized until the safety and dose escalation review committee reviews and evaluates the findings.

The sponsor will notify the investigator and IEC if the study is placed on hold, or if the sponsor decides to discontinue the study or development program.

The sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guidelines for GCP

7. VISIT PROCEDURES

[redacted]

7.1. Screening Period (5 to 8 weeks)

7.1.1. Screening Visit 1

Screening Visit 1 is to occur between Week -8 and Week -5. Subjects who do not fulfill all eligibility criteria will not be enrolled in the study.

Screening Visit 1 procedures for all subjects are as follows:

- Obtain informed consent before performing any study-related procedures, including Screening procedures
- Record medical history and demographics
- Verify inclusion and exclusion criteria for eligibility
- Measure body weight and calculate BMI
- Perform physical exam and neurological exam
- Perform 12-lead ECG
- Measure vital signs
- Record any concomitant medications
- Record any AEs

[redacted]

- Obtain blood samples for:
  - [redacted]
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Fasting lipid panel
  - Pregnancy test (female subjects only)

  - FSH (female subjects to confirm postmenopausal status only)
  - Coagulation
  - TSH and free T3 and T4
- Obtain urine sample for
  - Urinalysis
  - Urine drug screen

7.1.2. Screening Visit 2

Screening Visit 2 is to occur at least 4 weeks from Screening Visit 1 to determine whether subjects meet Inclusion Criterion 9 (i.e., AST, ALT, ALP, and total bilirubin must have 2 values 4 weeks apart that are within 20% of each other). Subjects who do not fulfill all eligibility criteria will not be enrolled in the study.

Screening Visit 2 procedures for all subjects are as follows:

- Verify inclusion and exclusion criteria for eligibility
- Record any concomitant medications
- Record any AEs
- Obtain blood samples for:
  - Chemistry (AST, ALT, ALP, and total bilirubin only)

For subjects with AST, ALT, ALP, or total bilirubin values from Screening Visits 1 and 2 that are not within 20% of each other, an unscheduled visit within the screening period may be conducted to repeat these assessments.

7.1.3. [redacted]

[redacted] procedures for all subjects are as follows:

- [redacted]
- [redacted]
- Record any concomitant medications
- Record any AEs
- Obtain blood samples for:
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Fasting lipid panel
  - Pregnancy test (female subjects only)
  - Coagulation

  - [redacted]

- Obtain urine sample for:
  - Urinalysis

7.2. Treatment Period (24 weeks)

7.2.1. [redacted]

[redacted] procedures for all subjects are as follows:

- Record medical history
- Verify inclusion and exclusion criteria for eligibility
- [redacted]
- Perform physical exam and neurological exam
- Perform 12-lead ECG [redacted]
- [redacted]
- Measure vital signs [redacted]
- Record any concomitant medications
- Record any AEs
- [redacted]
- Obtain blood samples for:
  - PK at up to [redacted]
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Fasting lipid panel
  - [redacted]
  - Coagulation
- Obtain urine sample for:
  - Urinalysis
  - Pregnancy test (female subjects only)
- Dispense study drug (1 mg etrasimod) and administer tablet at the clinic

7.2.2. [redacted]

[redacted] procedures for all subjects are as follows:

- [redacted]
- Perform physical exam and neurological exam

- Perform 12-lead ECG [redacted]
- Measure vital signs [redacted]
- Record any concomitant medications
- Record any AEs
- [redacted]
- Obtain blood samples for:
  - PK at up to [redacted]
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
- Obtain urine sample for:
  - Urinalysis
- Dispense study drug (1 mg etrasimod) and administer tablet at the clinic

7.2.3. [redacted] procedures for all subjects are as follows:

- [redacted]
- Perform physical exam and neurological exam
- Perform 12-lead ECG [redacted]
- Measure vital signs [redacted]
- Record any concomitant medications
- Record any AEs
- [redacted]
- Obtain blood samples for:
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Fasting lipid panel (Week 4 only)
  - Pregnancy test (female subjects only)
- Obtain urine sample for:
  - Urinalysis
- Dispense study drug (1 mg etrasimod) and administer tablet at the clinic

7.2.4. [redacted]

The safety and dose escalation review committee will review the PK and safety data from each PBC patient and will make individualized recommendations on whether a patient will remain at the 1 mg dose or escalate to the 2 mg dose at Week 12 as described in 5.5.

[redacted] procedures for all subjects are as follows:

- [redacted]
- Perform physical exam and neurological exam
- Record any concomitant medications
- Record any AEs

[redacted]

- Obtain blood samples for:
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Fasting lipid panel
  - Pregnancy test (female subjects only)
  - [redacted]
  - Coagulation
- Obtain urine sample for:
  - Urinalysis

[redacted] procedures for all subjects who dose escalate are as follows:

- Perform 12-lead ECG [redacted]
- [redacted]
- Measure vital signs [redacted]
- Obtain blood samples for:
  - PK [redacted]
- Dispense study drug (2 mg etrasimod) and administer tablet at the clinic

[redacted] procedures for all subjects who do not dose escalate are as follows:

- Perform 12-lead ECG [redacted]
- Measure vital signs [redacted]

- Obtain blood samples for:
  - PK [redacted]
- Dispense study drug (1 mg etrasimod) and administer tablet at the clinic

7.2.5. [redacted]

This visit will take place only for dose-escalated subjects.

[redacted] procedures for all subjects are as follows:

- [redacted]
- Perform physical exam and neurological exam
- Perform 12-lead ECG [redacted]
- Measure vital signs [redacted]
- Record any concomitant medications
- Record any AEs
- [redacted]
- Obtain blood samples for:
  - PK at up to [redacted]
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
- Obtain urine sample for:
  - Urinalysis
- Dispense study drug (2 mg etrasimod) and administer tablet at the clinic

7.2.6. [redacted]

[redacted] procedures for all subjects are as follows:

- [redacted]
- Perform physical exam and neurological exam
- Perform 12-lead ECG [redacted]
- Measure vital signs [redacted]
- Record any concomitant medications
- Record any AEs
- [redacted]
- Obtain blood samples for:
  - Chemistry, including ALP

  - Complete blood count and lymphocyte subsets
  - Pregnancy test (female subjects only)
  - Coagulation (Week 16 only)
- Obtain urine sample for:
  - Urinalysis

[redacted] procedures for all subjects who dose escalate are as follows:

- Dispense study drug (2 mg etrasimod) and administer tablet at the clinic

[redacted] procedures for all subjects who do not dose escalate are as follows:

- Dispense study drug (1 mg etrasimod) and administer tablet at the clinic

7.2.7. [redacted]

[redacted] procedures for all subjects are as follows:

- [redacted]
- Measure body weight and calculate BMI
- Perform physical exam and neurological exam
- Perform 12-lead ECG [redacted]
- Measure vital signs [redacted]
- Record any concomitant medications
- Record any AEs
- [redacted]
- Obtain blood samples for:
  - PK at [redacted]
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Fasting lipid panel
  - Pregnancy test (female subjects only)
  - [redacted]

  - Coagulation
- Obtain urine sample for
  - Urinalysis

7.3. Follow-Up Period

7.3.1. [redacted]

[redacted] procedures for all subjects are as follows:

- [redacted]
- Measure body weight and calculate BMI
- Perform physical exam and neurological exam
- Measure vital signs
- Record any concomitant medications
- Record any AEs
- Obtain blood samples for:
  - Chemistry, including ALP
  - Complete blood count and lymphocyte subsets
  - Total serum IgG and IgM, AMA and hsCRP

If the absolute peripheral lymphocyte count has not recovered to at least 80% of the baseline value, or reached normal ranges at the 2-week follow-up, the subject must return for weekly CBC tests until the absolute peripheral lymphocyte count has returned to at least these values.

8. DATA MANAGEMENT

8.1. Data Collection

All data (ECGs, clinical laboratory data, and all other study-related data) will be collected according to the sponsor/CRO's SOPs or according to study site standards, if applicable.

8.2. Data Coding

8.2.1. Adverse Events

AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self-limited fever, runny nose, cough, and scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). AEs will be regarded as 'pre-treatment' if they occur between screening and the time of administration of the first dose of etrasimod. All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'.

8.2.2. Concomitant Medications and Non-Drug Treatments

Due to the variability in how medications are recorded, a standard naming convention is required to tabulate this data effectively. A common method of standardization is to categorize medications by their Preferred Term (PT). Medications will be coded using the World Health Organization Drug Dictionary (WHO DD), Format C.

8.2.3. Medical History

Medical history will be coded using the most current MedDRA-version.

9. PLANNED STATISTICAL METHODS

[redacted]

Summary statistics will be provided to describe efficacy and safety measures. Confidence interval of key efficacy measures will be also produced for non-inferential comparisons with historical data.

9.1. Hypotheses

There are no formal hypothesis tests specified in this open-label study due to the lack of a control treatment group.

9.2. Sample Size and Power Calculations

There is no formal sample size estimation for this proof-of-concept open label study. A sample size of 20 subjects is reasonable to assess the efficacy and safety of etrasimod in the target population.

9.3. Analysis Populations

Efficacy endpoints will be analyzed in enrolled patients who have baseline and at least one post-baseline measure.

Safety endpoints will be analyzed in enrolled patients who received at least one dose of the study drug.

9.4. Demographics and Baseline Characteristics

All baseline patient characteristics of demographic data (age, height, weight, race), disease history, medical history (abnormalities only), physical examination (abnormalities only), and concomitant medications at study entry will be listed for all patients.

Demographic data will be summarized and tabulated. Continuous variables will be summarized using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be reported for all categorical data.

9.5. Efficacy Endpoints

- change from baseline to Week 12 and 24 in serum ALP concentration.
- change from baseline to Weeks 12 and 24 in:
  - Complete blood counts (including lymphocytes and subsets thereof).
  - hsCRP, ALT, AST, GGT, [redacted] C4 and [redacted] serum concentrations.
  - Total serum IgG, IgM, and AMA.
  - QoL, pruritus and fatigue (using the PBC-40 score and 5-D pruritus scales).
  - Ophthalmological examinations:
    - The Schirmer Test

[redacted]

9.6. Statistical Methods

9.6.1. Efficacy Analysis

There are no inferential comparisons for study endpoints. Summary statistical analyses will be performed for all efficacy measures. For proportion-based measures, N, frequencies, proportion and its 95% confidence interval (CI) will be produced. For continuous measure, N, mean, median, range, and SD will be produced for observed values, and additional 95% CI for change or percent change from baseline will be produced if applicable.

9.6.2. Subgroup Analyses

Exploratory analysis of main study endpoints will be performed in subset of patients of medical interests, such as patient demographics, baseline ALP levels, baseline disease characteristics, biomarker, previous disease treatment received, etc. [redacted]

9.6.3. Pharmacokinetic Analysis

Pharmacokinetic parameters of etrasimod, and its metabolites (if possible) will be calculated using non-compartmental methods. [redacted]

Individual etrasimod plasma concentrations at specified time points will be listed for each patient. Individual plasma concentration-time points of etrasimod will be plotted on both a linear and a semi-logarithmic scale for each dose level. [redacted]

9.6.4. Interim Analysis

An informal interim analysis of safety and efficacy will be performed when up to half the patients have finished 12 weeks of treatment.

9.7. Safety Analysis

Safety and tolerability will be assessed by a review of all safety parameters including AEs, laboratory safety parameters, [redacted] vital signs, and ECG. AEs will only be presented as summary tabulations. When assessing change from baseline, a baseline measurement is also required. Baseline for the safety analysis is defined as the average of the pre- dose measurements. No missing data will be imputed for the safety analysis. For continuous variables, summary statistics (N, mean [or median], SD, mean [or median] change/percent change) and 95% CI will be produced if applicable; for proportion-based measures, N, frequencies, proportion and its 95% CI will be produced.

9.7.1. Adverse Events

AEs will be coded using the most current MedDRA and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. AEs will be regarded as ‘pre-treatment’ if they occur between screening and the time of administration of the first dose of etrasimod. All other AEs that occur after the first dose of study medication will be considered to be ‘treatment-emergent’.

Pre-treatment and treatment-emergent AEs will be listed by patients, in terms of seriousness, severity and intensity (assessed according to the CTCAE v4.03; 14Jun2010 definitions [31]). TEAEs will be classified according to system organ class.

9.7.2. Physical Examinations

Physical examination results (abnormalities only) at each study visit will be listed.

9.7.3. Concomitant Medication

Pre-treatment and concomitant medication administered during the study will be listed. Concomitant medications will be coded using the WHO-DRUG Dictionary.

9.7.4. Vital Signs

Individual vital sign measurements will be summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in vital sign measurements. Baseline is defined as the last pre-dose measurement.

[redacted]

9.7.6. Clinical Laboratory Values

Individual lab values will be listed by visit, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in hematological parameters (e.g., lymphocytes) or other parameters. Baseline is defined as the average of the pre-dose measurements. A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

9.7.7. Safety ECG (12-lead ECG)

Individual safety ECG (12-lead) values will be listed by visit, and summarized using descriptive statistics. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF. Post-screening ECGs will be compared with the baseline ECG. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

10. REGULATORY REQUIREMENTS

10.1. Pre-Study Documentation

The sponsor must receive the following documentation prior to initiation of the trial:

- Protocol signature page signed and dated by the principal investigator (PI)
- Curriculum vitae of the PI and sub-investigators, updated within last two years
- Current medical licenses for the PI and all sub-investigators
- Financial disclosure form signed by the PI and all sub-investigators if applicable to local regulations
- Copy of the IEC (HREC) approval letter for the study and approved ICF
- IEC (HREC) membership list
- Copy of the regulatory authority approval (if applicable as per local guidelines)

Additional country-specific documentation may be required per international regulatory authorities.

10.2. Investigator Obligations

The PI is responsible for ensuring that all study site personnel, including sub-investigators and other study staff members, adhere to all country regulatory requirements and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. The PI will be responsible for the patient's compliance to the study protocol. The PI is responsible for providing the sponsor an adequate final report shortly after he/she completes participation in the study, in accordance with ICH Guidelines E6, E2A, and E8.

10.3. Patient Confidentiality

All information obtained during the conduct of the study with respect to the patients is regarded as confidential. This is detailed in the written information provided to the patient. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the ICF signed by the patient. The study data shall not be disclosed to a third party without the written consent of the sponsor or designee.

10.4. Informed Consent

According to ICH Guideline E6, "*Good Clinical Practice: Consolidated Guidance*", the investigator will obtain and document informed consent for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The patient's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The informed consent should include all the elements outlined in Section 4.8.10 of ICH Guideline E6.

10.5. Independent Ethics Committee (IEC) Human Research Ethics Committee (HREC)

This protocol and relevant supporting data are to be submitted to the appropriate IEC (HREC) for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IEC prior to implementation of the change. The sponsor must receive a letter documenting the IEC approval prior to initiation of the study. If applicable to local regulations the following may also apply: the PI is also responsible for informing the IEC of the progress of the study and for obtaining annual IEC renewal. The IEC must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IEC in writing of any SAE or any unexpected AE according to ICH guidelines.

11. PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

11.1. Study Documentation

The PI and study staff have the responsibility of maintaining a comprehensive study-related documentation. These files must be available for inspection by the sponsor, representatives of the sponsor, the IEC, and international regulatory authorities at any time, and should consist of the following elements:

- Patient files, including but not limited to the completed electronic case report forms (eCRFs), supporting source documentation from the medical record including laboratory data and the ICF;
- Regulatory files, containing the protocol with all amendments and investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IEC and sponsor; and
- Drug accountability files, including a complete account of the receipt and disposition of the study medication (test article).

Records are to be available for until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (or if the application is not approved or never submitted, 2 years after the last shipment and delivery of the material and the appropriate competent regulatory authorities are notified). The sponsor will provide written notification when it is appropriate for the investigator(s) to discard the study-specific documents referenced above.

11.2. Protocol Interpretation and Compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the PI and his or her staff prior to the time of study initiation. The Sponsor and PI will follow all reasonable means to resolve any differences of opinion of matters of eligibility, toxicity and other endpoints. In the event that a resolution cannot be reached then one or both parties may seek to terminate the study following the provisions outlined in the Clinical Trials Agreement.

11.3. Study Monitoring

The sponsor or a contracted monitor will visit the study center periodically to monitor adherence to the protocol, compliance with ICH guidelines, adherence to applicable regulations, and the maintenance of adequate and accurate clinical records. Case report forms will be reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The monitor will be permitted to access patients' complete medical records, laboratory data, and other source documentation as needed to monitor the trial appropriately.

12. PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as outlined in the protocol entitled "An Open-label, Pilot, Proof of Concept Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Etrasimod (APD334) in Patients with Primary Biliary Cholangitis" in accordance with regulatory guidelines, ICH GCP Guidelines and the Declaration of Helsinki; and all applicable government regulations.

These guidelines and regulations include, but are not limited to:

- Permission to allow the sponsor, or designee, or country specific regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures patient confidentiality. If this study is to be inspected by a regulatory agency, the sponsor and CRO should be notified as soon as possible.
- Submission of the proposed clinical investigation, including the protocol and the consent form, to a duly constituted IEC for approval, and acquisition of written approval for each prior to the use of the study drug.
- Use of written informed consent that is obtained prior to administration of study drug or any non-routine procedures that involve risk, and that contains all the elements of consent as specified in the federal regulations and has been previously approved by the sponsor and the IEC.
- Submission of any proposed change in the protocol to the IEC using a signed formal amendment document approved by the sponsor. Any proposed changes to the protocol require that the informed consent also reflect such changes and that the revised informed consent be approved as determined by the IEC.
- Documentation and explanation of individual protocol deviations on the appropriate CRF page or in letters to the sponsor.
- Submission of written reports of SAEs to Arena Pharmaceuticals, Inc. or designated CRO within 24 hours after the investigator's initial receipt of the information.
- Submission of reports of SAEs, as outlined in the protocol, to the IEC within 15 calendar days of their disclosure.
- Submission of timely progress reports to the IEC and sponsor at appropriate intervals on a schedule determined by the IEC.
- Maintenance of appropriate records: ICH guidelines require an investigator to prepare and maintain adequate and accurate case histories designed to record all observations and other data (such as study drug accountability) pertinent to the investigation on each individual enrolled in the study. These records must be maintained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

In addition, I agree to provide all the information requested in the CRF in a manner to assure legibility and accuracy. To this end, I shall carefully follow the instructions for completing CRFs and approve with signature.

I also agree that all information provided to me by the sponsor, including protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical

personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB/IEC. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the PI, or in confidence to the IRB/IEC or other legally constituted authority.

Principal Investigator **Date**

Printed Name

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SPONSOR PROTOCOL SIGNATURE PAGE

Protocol Title: An Open-label, Pilot, Proof of Concept Study to Evaluate the Safety, Tolerability, and Efficacy of Oral Etrasimod (APD334) in Patients with Primary Biliary Cholangitis

This study will be conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) (E6).

Protocol Number: APD334-010

Arena Pharmaceuticals, Inc. Signatures:

Electronic Signature Appended

Appendix 1 Summary of Changes by Amendment

Summary of Changes for Amendment 4.0 Dated 27 June 2018

Protocol APD334-010 was amended to allow additional tests to confirm PBC diagnosis, lower the ALP threshold from >1.67 × ULN to >1.5 × ULN to be consistent with the Paris II ALP criteria, add AE and concomitant assessments to Screening Visit 2, and change the definition of the safety baseline.

Revised text in Amendment 4.0 is indicated in bold font, and text deleted from Version 3.0 is crossed out in the table below. Minor/editorial changes are not listed in the summary table.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	1. Males or females aged 18 to 80 years (inclusive) at the time of screening, with confirmed PBC diagnosis based upon at least 2 of 3 criteria: • AMA titer >1:40	1. Males or females aged 18 to 80 years (inclusive) at the time of screening, with confirmed PBC diagnosis based upon at least 2 of 3 criteria: • AMA titer >1:40 **on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies (anti-GP210 and/or anti-SP100)**	We have included additional tests confirming PBC diagnoses allowing for ELISA and for other PBC-specific auto-antibodies in cases whereby the AMA titer is low. Per AASLD guidelines, these tests are indicative of PBC diagnoses.[32]
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	[redacted]		
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	~~3. Be on a stable dose of UDCA for at least 3 months~~ prior to screening	**2. Use of UDCA for at least 6 months** prior to screening **(stable dose for at least 3 months immediately prior to screening)**	UDCA dosing information is the same as in amendment 3 but consolidated under one criteria for amendment 4 for clarity.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	~~5.~~ Patients must have the following laboratory parameters at screening ALP >1.~~67~~ × ULN but <10 × ULN (at all screening visits)	**4.** Patients must have the following laboratory parameters at screening ALP >1.**5** × ULN but <10 × ULN (at all screening visits)	The ALP threshold for eligibility is being lowered from >1.67 × ULN to >1.5 × ULN to be consistent with the Paris II ALP criteria, which is used to predict prognosis in early PBC.[33] An ALP level of >1.5 × ULN would still allow for detection of an efficacy signal in this safety study.
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	[redacted]		
Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria	[redacted]		
Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria			

Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria	[redacted]		
3.3: End of Study (Table 1)	[redacted]		
3.3: End of Study (Table 1)	*New text*	*Added AE and concomitant assessments at Screen 2.*	The AE and concomitant assessments were added to Screening Visit 2 for consistency.
5.2.1: Dose-Stopping Rules	*New text*	**As described in 3.1, at the discretion of the PI, the dose of etrasimod may be adjusted from 2 mg q.d. back to 1 mg q.d. if deemed necessary.**	The text was added to be consistent with text already included in the synopsis.
6.9.5: Blood Volume	The total blood volume collected ~~to cover all sampling procedures as required by the outline~~ in Schedule of Procedures and Visits [Table 1])~~,~~ is ~~up~~ to ~~270 mL during the study~~	The total blood volume collected **from each patient participating in the study (according to the sampling described** in **the** Schedule of Procedures and Visits [Table 1]) is **estimated** to **be 340 mL, but will not exceed 500 mL.**	The blood volume section was updated to reflect differences in collection tubes and sample processing and analysis between countries.

6.15: Adverse Events Assessments	Patients will be monitored from ICF signature to ~~2 weeks~~ after the last dose of study drug for AEs to the study drug and/or procedures.	Patients will be monitored from ICF signature to **30 days** after the last dose of study drug for AEs to the study drug and/or procedures.	The text was updated to reflect that AEs reported following study medication administration up to 30 days after the last medication intake will be reported.
7.1.2: Screening Visit 2	Screening Visit 2 procedures for all subjects are as follows: • Verify inclusion and exclusion criteria for eligibility	Screening Visit 2 procedures for all subjects are as follows: • Verify inclusion and exclusion criteria for eligibility • **Record any concomitant medications** • **Record any AEs**	The AE and concomitant assessments were added to Screening Visit 2 for consistency.
7.2.7: Week 24 ([redacted]) End of Treatment / Early Withdrawal	• Obtain blood samples for: ○ PK [redacted]	• Obtain blood samples for: ○ PK [redacted]	The text was corrected to be consistent with the PK sampling strategy for this visit discussed elsewhere in the protocol
9.7: Safety Analysis	Baseline for the safety analysis is defined as the ~~last~~ pre- dose measurement.	Baseline for the safety analysis is defined as the **average of the** pre-dose measurements.	The average value of the measurements prior to dosing will be used for baseline rather than using only one baseline measurement. This will provide a more accurate assessment of baseline.
9.7.6: Clinical Laboratory Values	Baseline is defined as the ~~last~~ pre-dose measurement.	Baseline is defined as the **average of the** pre-dose measurements.	The average value instead of the last measurement will be used for baseline to provide a more accurate assessment of baseline.

Summary of Changes for Amendment 3.0 Dated 14 March 2018

Protocol APD334-010 was amended to add Screening Visit 2 to the study design to ensure the repeat assessment of liver enzyme values are available in time for enrollment. Additional changes introduced in this amendment include:

- Clarifying that tablets are to be taken at the clinic
- Revising the fasting period to address study visits where study medication is not administered
- Clarifying that the vital signs and ECG [redacted]
- Specifying that [redacted] C4 will not require additional blood sampling or procedures and will be determined using back-up PK samples
- Adding a collection window for PK blood samples, vital signs, and ECG measurements
- Changing the abbreviated/interim physical exam to full examinations
- Changing the medical monitor
- Clarifying that this protocol is a Phase 2 study, not a Phase 1 study
- Including that Protocol Amendment 2 was never released to the site

Revised text in Amendment 3.0 is indicated in bold font, and text deleted from Version 2.0 is crossed out in the table below. Minor/editorial changes are not listed in the summary table.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Global Change	*Screening period was 4 to 8 weeks before baseline visit.*	*Screening period is now 5 to 8 weeks before the baseline visit.*	The screening period duration was changed from 4-8 to 5-8 weeks to allow for time to evaluate liver enzyme values.
Title page Synopsis: Study Phase	Study Phase: ~~I/II~~	Study Phase: 2	This is a Phase 2 study conducted in PBC patients. Phase 1 was indicated in error.
Title Page	[redacted] MD~~, PhD~~ [redacted]~~, Clinical Development~~ Arena Pharmaceuticals, Inc. ~~6154 Nancy Ridge Drive~~ ~~San Diego, California 92121, US~~ Tel: [redacted] Email: [redacted]	[redacted], MD **Medical and Safety** [redacted] Arena Pharmaceuticals, Inc. **Gotthardstrasse 3** **CH – 6300 Zug** **Switzerland** Tel: [redacted] Email: [redacted]	The Arena medical monitor responsibilities will be assumed by [redacted]
Title Page	Amendment 02: 07 February 2018	Amendment 02: 07 February 2018 **(Not released to sites)**	Protocol Amendment 2 was never released to the sites as it was determined additional clarifications were required to ensure study procedures are completed appropriately.

Synopsis: Test Product, Dose and Mode of Administration	[redacted]		The protocol was clarified to state that tablets are to be taken at the clinic. The [redacted] period was revised to address study visits where study medication is not administered.
Synopsis: Screening Period (5 to 8 weeks before baseline visit) 3.1: Overall Study Design and Plan	Each patient will be asked to visit the study site for screening assessments ~~4 to~~ 8 weeks prior to the planned start of the treatment (Day 1).	Each patient will be asked to visit the study site **at least 2 times** for screening assessments **within the** 8 weeks prior to the planned start of the treatment (Day 1). **Screening Visit 1 is to occur between Week -8 and Week -5. Screening Visit 2 is to occur at least 4 weeks from Screening Visit 1. For patients with ALP, ALT, AST, or total bilirubin values from Screening Visits 1 and 2 that are not within 20% of each other (see Inclusion Criterion 9), an unscheduled visit within the screening period may be conducted to repeat these assessments.**	The screening period duration was changed from 4-8 to 5-8 weeks to allow for time to evaluate liver enzyme values. Screening Visit 2 was added to the study design to ensure the repeat assessment of liver enzyme values are available in time for enrollment (see Inclusion Criterion 9).
Synopsis: Treatment period (24 weeks) 3.1: Overall Study Design and Plan	[redacted]		

Synopsis: Treatment period (24 weeks) 3.1: Overall Study Design and Plan	Patients with dose escalation [redacted] (6.13), and vital signs and ECG monitoring performed [redacted]	Patients with dose escalation [redacted] (6.13), and vital signs and ECG monitoring performed [redacted]	The text was revised to clarify that the vital signs and ECG monitoring periods [redacted]
Synopsis: Dose-stopping rules	The patient will be monitored [redacted] after the intake of study medication doses at the clinic as per the Schedule of Procedures and Visits (Table 1).	The patient will be monitored [redacted] after the intake of study medication doses at the clinic as per the Schedule of Procedures and Visits (Table 1).	The text was revised to clarify that the ECG [redacted]
Synopsis: Inclusion Criteria 4.1: Inclusion and Exclusion Criteria	*New text*	**Inclusion and exclusion criteria that refer to an assessment being performed "at screening" are referring to Screening Visit 1 unless specified otherwise.**	Given that this amendment introduces a second screening visit, a distinction between the two visits was made.
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	5. Patients must have the following laboratory parameters at screening • ALP >1.67 x ULN but <10 x ULN • ALT and AST <5 x ULN • Total bilirubin <ULN	5. Patients must have the following laboratory parameters at screening • ALP >1.67 x ULN but <10 x ULN **(at all screening visits)** • ALT and AST <5 x ULN **(at all screening visits)** • Total bilirubin <ULN **(at all screening visits)**	Given that this amendment introduces a second screening visit and that these analytes are measured at both visits, these thresholds must now be met at all screening visits.
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	9. AST, ALT, ALP, ~~or~~ total bilirubin must have 2 values 4 weeks apart that are within 20% of each other.	9. AST, ALT, ALP, **and** total bilirubin must have 2 values **at least** 4 weeks apart that are within 20% of each other.	The criterion was corrected from "or" to "and" and the window between assessments was updated to reflect the new visit window during screening.

Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria	[redacted]		
Synopsis: Pharmacokinetic Assessments 3.3: End of Study 6.13: Pharmacokinetic Assessments	*New text*	**All PK samples are to be collected [redacted] of the scheduled timepoint.**	A collection window for PK samples was added to allow some flexibility in collecting samples and to minimize the likelihood of protocol deviations.
3.1: Overall Study Design and Plan	*The original Figure 1 (Schematic of APD334-010 Study Design) had one screening visit and it looked like treatment started on Day -1.*	*Figure 1 (Schematic of APD334-010 Study Design) was revised to include footnote a, which states Screening Visit 1 is to occur between Week -8 and Week -5. Screening Visit 2 is to occur at least 4 weeks from Screening Visit 1. For patients with ALP, ALT, AST, or total bilirubin values from Screening Visits 1 and 2 that are not within 20% of each other (see Inclusion Criterion 9), an unscheduled visit within the screening period may be conducted to repeat these assessments. The treatment bars were revised so that treatment starts at Day 1.*	Screening Visit 2 was added to the study design to ensure the repeat assessment of liver enzyme values are available in time for enrollment (see Inclusion Criterion 9).
3.3: End of Study	*New text*	*Added Screening Visit 2, the associated assessments, footnote a and footnote 8 to Table 1 (Schedule of Procedures and Visits).*	Table 1 (Schedule of Procedures and Visits) was updated to reflect the new visit schedule during screening.
3.3: End of Study	[redacted] *C4 evaluations were included in Table 1 (Schedule of Procedures and Visits).*	[redacted] *C4 evaluations were removed from Table 1 (Schedule of Procedures and Visits).*	Deleted reference to these exploratory tests in Table 1 (Schedule of Procedures and Visits) as this section is used to inform sites on study procedures; C4/[redacted] will not require additional blood sampling.

3.3: End of Study	[redacted]		The protocol was clarified to state that tablets are to be taken at the clinic. The [redacted] period was revised to address study visits where study medication is not administered.
3.3: End of Study	~~1. Interim/abbreviated physical exam only.~~	*Deleted text*	The interim/abbreviated physical exam will be replaced with a full physical exam as this was the original intention.

3.3: End of Study	2. Vital signs and 12-lead ECG will be captured [redacted] for those patients with dose escalation, vital signs and ECG monitoring will be performed [redacted] for those patients without dose escalation, ECG monitoring will be performed [redacted]. For the rest of clinical visits ([redacted]), vital signs and 12-lead ECG will be captured [redacted]	2. Vital signs and 12-lead ECG will be captured [redacted], for those patients with dose escalation, vital signs and ECG monitoring will be performed [redacted] for those patients without dose escalation, **vital signs and** ECG monitoring will be performed [redacted], **vital signs and ECG monitoring will be performed** [redacted]. For the rest of clinical visits ([redacted]), vital signs and 12-lead ECG will be captured at [redacted]	The text was revised to clarify that the vital signs and ECG [redacted] As there is no study drug dose at the [redacted] visit, vital signs and ECG measurements at this visit were corrected from [redacted]
3.3: End of Study	*New text*	**2. Vital signs and ECGs are to be measured [redacted] of the scheduled timepoint.**	A window for vital signs and ECG measurements was added to allow some flexibility in collecting data and to minimize the likelihood of protocol deviations.

5.2: Dosage, Administration and Accountability	~~On~~ [redacted] ~~the patients will come to the clinic for safety and/or PK monitoring.~~ [redacted]	[redacted]	The protocol was clarified to state that tablets are to be taken at the clinic. The [redacted] period was revised to address study visits where study medication is not administered.
6.5: Vital Signs	*New text*	**Vital signs are to be measured [redacted] of the scheduled timepoint.**	A window for vital signs measurements was added to allow some flexibility in collecting data and to minimize the likelihood of protocol deviations.
6.6.3: ECG Assessment	*New text*	**ECGs are to be measured [redacted] of the scheduled timepoint.**	A window for ECG measurements was added to allow some flexibility in collecting data and to minimize the likelihood of protocol deviations.
6.6.3: ECG Assessment	[redacted]		

6.9.1: List of Laboratory Parameters	~~Serum~~ [redacted] hsCRP ~~7 alpha hydroxy 4 cholesten 3 one (C4)~~	hsCRP	Deleted reference to serum [redacted] and C4 tests in this section as this section is used to inform sites on study procedures; C4/[redacted] will not require additional blood sampling.
6.9.5: Blood Volume	The total blood volume collected to cover all sampling procedures (as required by the outline in Schedule of Procedures and Visits [Table 1]), is up to 2~~15~~ mL during the study.	The total blood volume collected to cover all sampling procedures (as required by the outline in Schedule of Procedures and Visits [Table 1]), is up to 2**70** mL during the study.	The blood volume was revised to reflect changes to the study design and assessments.
6.13: Pharmacokinetic Assessments	An additional PK blood sample will be collected, if possible, at the time of any intolerable AE or SAE.	An additional PK blood sample will be collected, if possible, at the time of any intolerable AE **(an AE leading to study drug discontinuation)** or SAE.	The text was expanded upon to add the definition of an intolerable AE.
6.14: C4 and [redacted]	*New text*	**C4 and [redacted] may be analyzed, if deemed necessary by the Sponsor, depending on ALP levels throughout the course of the study for exploratory objectives. For this purpose, back up PK samples will be used.**	This section was created to inform sites on study procedures that will not require additional blood sampling.
6.15.1: Adverse Event Reporting	Monitoring of ongoing AEs will be continued up to ~~2 weeks~~ after study medication administration.	Monitoring of ongoing AEs will be continued up to **30 days** after study medication administration.	The text was corrected so that the duration of the monitoring period is consistent with the rest of the protocol.
7: Visit Procedures	*New section*	*Added a list of procedures for each visit to reflect the information in Table 1 (Schedule of Procedures and Visits)*	The Visit Procedures section was added to clarify which assessments are to be performed at each visit.
[redacted]			

Appendix 2: 5-D Pruritus Scale	*Appendix contained an example of the 5-D Pruritus Scale*	*The appendix and 5-D Pruritus Scale example were deleted.*	The 5-D Pruritus Scale will be provided to clinics outside of the protocol.
Appendix 3: PBC-40 Quality of Life Assessment	*Appendix contained an example of the PBC-40 Quality of Life Assessment*	*The appendix and PBC-40 Quality of Life Assessment example were deleted.*	The PBC-40 Quality of Life Assessment will be provided to clinics outside of the protocol.

Summary of Changes for Amendment 2.0 Dated 07 February 2018

Protocol APD334-010 was amended to primarily add or clarify criteria and procedures to improve patient safety.

Revised text in Amendment 2.0 is indicated in bold font, and text deleted from Version 1.0 is crossed out in the table below. Minor/editorial changes are not listed in the summary table.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Global Change	*The screening period was up to 4 weeks long, and the total study duration was up to 30 weeks.*	*The screening period is now 4 to 8 weeks long, and the total study duration is now up to 34 weeks.*	Baseline values should be established by at least two samples obtained at least 4 weeks to 8 weeks apart to account for disease-related changes in liver enzymes.
Global Change	dose escalation committee	**safety and** dose escalation committee	The name of the dose escalation committee was revised to the safety and dose escalation committee to better reflect its function.
Synopsis: Dose-stopping Rules	Any of the following findings in patient~~s~~ during treatment will lead to a stop in etrasimod dosing:	Any of the following findings in **a** patient during treatment will lead to a stop in etrasimod dosing **in the affected patient**:	The text was rephrased to make it clear that the stop in dosing will occur only in the affected patient.
Synopsis: Dose-stopping Rules 5.2.1: Dose-stopping Rules	2. ~~ALT/AST >3 x baseline level and >ULN, or~~ ~~Total bilirubin >2 x baseline level and >1.8 mg/dL (30.8 umol/L)~~	2. **Clinical evidence of drug-induced liver injury (DILI; as described in 6.15)**	This dose-stopping rule was revised to reflect the new study drug discontinuation for suspected DILI criteria added to this version of the protocol.
Synopsis: Dose-stopping Rules 6.15.1: Close Observation for Possible DILI	*New text*	**Close Observation for Possible DILI:** **It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. Close observation is mandatory for any study subject who meets one or**	To further protect patient safety, a detailed clinical management plan is included to evaluate and respond to cases of new elevations (or new elevations from baseline) in transaminases or tests of liver function.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
		more of the following "possible DILI" laboratory criteria: • **ALT or AST that is <ULN at baseline, followed by ALT or AST increase to >3 x ULN** • **ALT or AST that is >ULN at baseline, followed by ALT or AST increase to >2 × baseline** • **ALP >2 × baseline** • **Total bilirubin >1.5 × ULN**	
Synopsis: Dose-stopping Rules 6.15.1: Close Observation for Possible DILI	*New text*	**Close observation includes:** • **Repeating liver enzyme and serum bilirubin tests within 48-72 hours. Then, repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities resolve, abnormalities stabilize, or the study drug has been discontinued and the subject is asymptomatic.** • **Obtaining a more detailed history of symptoms and prior or concurrent diseases.** • **Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.**	To further protect patient safety, a detailed clinical management plan is included to evaluate and respond to cases of new elevations (or new elevations from baseline) in transaminases or tests of liver function.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
		• **Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.** • **Obtaining a history of exposure to environmental chemical agents.** • **Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).** • **Considering consultations, imaging studies, and/or therapeutic interventions, as required.**	
Synopsis: Dose-stopping Rules 6.15.2: Study Drug Discontinuation for Suspected DILI	*New text*	**<u>Study Drug Discontinuation for Suspected DILI:</u>** **Should any patient who meets "possible DILI" laboratory criteria have persistence or worsening of lab data (i.e., ALT, AST, ALP, and/or total bilirubin) after one week of close observation, study drug must be discontinued. In addition, immediate study drug discontinuation is mandatory for any study patient who meets one or more of the following "suspected DILI" clinical criteria:**	To further protect patient safety, a detailed clinical management plan is included to evaluate and respond to cases of new elevations (or new elevations from baseline) in transaminases or tests of liver function.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
		• **ALT or AST <2 × ULN at baseline, followed by ALT or AST increase to >5 × baseline** • **ALT or AST ≥2 × ULN but <5 × ULN at baseline, followed by ALT or AST increase to >3 × baseline** • **ALT or AST increase to >2 × baseline AND concomitant total bilirubin increase to >2 × baseline** • **ALT or AST increase to >2 × baseline AND concomitant INR increase >0.2** • **Clinical signs and symptoms of liver inflammation, including but not limited to fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, jaundice, icterus, and/or eosinophilia (>5%)**	
Synopsis: Dose-stopping Rules	[redacted]		
Synopsis: Dose-stopping Rules 6.6.3: ECG Assessment	[redacted]		

Section	Amendment 1.0	Amendment 2.0	Reason for Change
	[redacted]		
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	1. Males or females aged 18 to ~~75~~ years (inclusive) at the time of screening, with confirmed PBC	1. Males or females aged 18 to **80** years (inclusive) at the time of screening, with confirmed PBC	The upper limit of the age range for inclusion into the study was increased from 75 to 80 years to increase the number of subjects

Section	Amendment 1.0	Amendment 2.0	Reason for Change
	diagnosis based upon at least 2 of 3 criteria:	diagnosis based upon at least 2 of 3 criteria:	eligible for study participation. Safety-related criteria already included in the study will exclude elderly subjects who are not appropriate for this study.
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	2. Inadequate response to UDCA defined ~~by an~~ ALP >1.67 × ULN after 6 months of UDCA ~~at a minimum dose of 13 mg/kg/day~~	2. Inadequate response to UDCA defined **as** ALP >1.67 × ULN after 6 months of UDCA **therapy**	The UDCA dose required to meet study inclusion was removed to better reflect clinical practices.
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	3. Be on a stable dose of UDCA for at least ~~6~~ months prior to screening	3. Be on a stable dose of UDCA for at least **3** months prior to screening	For inclusion in the study, a patient must have had an inadequate response to UDCA after 6 months of therapy but only on a stable dose for 3 months. This timeframe is suitable to demonstrate that the patient's disease state is fairly stable at the time of screening.
Synopsis: Inclusion Criteria 4.1.1: Inclusion Criteria	[redacted]		
Synopsis: Inclusion Criteria			

Section	Amendment 1.0	Amendment 2.0	Reason for Change
	[redacted]		
Synopsis: Exclusion Criteria 4.1.1: Inclusion Criteria	*New text*	**9. AST, ALT, ALP, or total bilirubin must have 2 values 4 weeks apart that are within 20% of each other.**	A criterion requiring subjects to have stable liver enzymes and bilirubin concentrations during screening was added to exclude subjects with evidence of worsening liver function.
Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria	2. History or evidence of clinically significant hepatic decompensation: [redacted]	2. History or evidence of clinically significant hepatic decompensation: [redacted]	The symptoms and clinical presentation of clinically significant hepatic decompensation were clarified.
Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria	[redacted]		
Synopsis: Exclusion Criteria 4.1.2: Exclusion Criteria	[redacted]		

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis: Pharmacokinetic Assessments 6.13 Pharmacokinetic Assessments	Patients will have a serial PK sampling [redacted]	Patients will have a serial PK sampling [redacted]	PK sampling was expanded in an attempt to fully characterize the PK profile of etrasimod in PBC patients.
3.1: Overall Study Design and Plan	The trial will include adult patients, 18-~~75~~ years of age, with a confirmed PBC diagnosis, and who had an inadequate response to UDCA.	The trial will include adult patients, 18-**80** years of age, with a confirmed PBC diagnosis, and who had an inadequate response to UDCA.	The upper limit of the age range for inclusion into the study was increased from 75 to 80 years to increase the number of subjects eligible for study participation. Safety-related eligibility criteria already included in the study will exclude elderly subjects who are not appropriate for this study.
3.3: End of Study, Table 1	[redacted]		

Section	Amendment 1.0	Amendment 2.0	Reason for Change
3.3: End of Study, Table 1 (footnote 2)	Blood samples for PK will be collected [redacted]	Blood samples for PK will be collected [redacted]	PK sampling was expanded to help fully characterize the PK profile of etrasimod in PBC patients.
3.3: End of Study, Table 1 (footnote 3)	Vital signs and 12-lead ECG will be captured [redacted] for those patients with dose escalation, vital signs and ECG monitoring will be performed [redacted].	Vital signs and 12-lead ECG will be captured [redacted] for those patients with dose escalation, vital signs and ECG monitoring will be performed [redacted] **for those patients without dose escalation, ECG monitoring will be performed [redacted] For the rest of clinical visits ([redacted]),**	Additional vital signs and 12-lead ECG evaluations [redacted] (for patients with dose escalation) were added to assess the effect of etrasimod on these parameters at steady state.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
		vital signs and 12-lead ECG will be captured [redacted].	
3.3: End of Study, Table 1 (footnote 3)	*New text*	**Typically, all safety ECGs will be obtained as single tracings, with the exception of the pretreatment ECG obtained on Day 1, which is a triplicate recording.**	This information is already stated in Section 6.6.1 (ECG Equipment) and was added to Table 1 for completeness.
3.3: End of Study, Table 1 (footnote 4)	[redacted]		
5.2.1: Dose-stopping Rules	~~The investigator must stop the dosing of etrasimod after any of the following findings in patients during treatment:~~	**Any of the following findings in a patient during treatment will lead to a stop in etrasimod dosing in the affected patient:**	The text was rephrased to make it clear that the stop in dosing will occur only in the affected patient.
6.6.3: ECG Assessment	[redacted]		

[redacted]

Section	Amendment 1.0	Amendment 2.0	Reason for Change
6.9: Clinical Laboratory Tests	Tests will be performed in the ~~local~~ laboratory ~~as per study site standards~~.	Tests will be performed in the **central** laboratory. **If the patient lives in a remote area, laboratory testing for close observation for possible DILI may be performed locally and the results promptly communicated to the clinic.**	Clarified that a local laboratory may be used for patients who live in remote areas for DILI monitoring to allow for a more rapid assessment of liver function.
6.9.1: List of Laboratory Parameters	[redacted]		
6.9.5: Blood Volume	The total blood volume collected to cover all sampling procedures (as required by the outline in Schedule of Procedures and Visits [Table 1]), is up to ~~200~~ mL during the study.	The total blood volume collected to cover all sampling procedures (as required by the outline in Schedule of Procedures and Visits [Table 1]), is up to **215** mL during the study.	The blood volume was updated to account for the 6 optional PK samples added to this amendment
6.15 Drug-Induced Liver Injury (DILI) Surveillance	*New text*	**In July 2009, the FDA released a Guidance for Industry entitled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," which reviews the importance of DILI surveillance in drug development. DILI has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years, and hepatotoxicity discovered after approval for marketing has limited the use of many drugs. Furthermore, the guidance addresses how laboratory measurements that signal the potential for DILI can be obtained and evaluated during drug development.**	Background information regarding the importance of DILI monitoring was added to provide context for the clinic staff.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
		Given the fact that all subjects enrolled in this study have pre-existing liver disease (i.e., PBC) and baseline elevations in laboratory tests of liver health (ALP, ALT and/or AST), DILI surveillance is of critical importance to patient safety. Therefore, in collaboration with the FDA and after careful consideration of the principles outlined in the DILI guidance, the sponsor has established procedures to ensure early detection of possible DILI and study drug discontinuation in the context of suspected DILI.	
6.18: Study and Site Discontinuation	*New text.*	**Additionally, if more than three patients develop a CTCAE grade 3 or higher event in the same category, or if three or more patients meet one of the individual stopping rules, the safety and dose escalation review committee (5.5) will convene to evaluate the findings. Further, dosing will be stopped in randomized patients and no new patients will be randomized until the safety and dose escalation review committee reviews and evaluates the findings.**	Expanded upon the definition of the original stopping criteria "incidence or severity of AEs in this or other studies indicating a potential hazard to patients."
[redacted]			

Section	Amendment 1.0	Amendment 2.0	Reason for Change
12: References	[redacted]		

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Title: [redacted] Clinical Development
Date: Thursday, 28 June 2018, 07:52 AM Pacific Daylight Time
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