CLINICAL PROTOCOL

A Phase 2 Open Label Proof-of-Concept Study of HTD1801 in Adult Subjects with Primary Biliary Cholangitis (PBC) and an Inadequate Response to Standard Therapy (PRONTO-PBC)

Protocol HTD1801.PCT013

IND 136137

NCT04604652

Study Sponsor: HighTide Biopharma Pty. Ltd.
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CONFIDENTIAL

SIGNATURES OF APPROVAL FOR PROTOCOL HTD1801.PCT013

Title: A Phase 2 Open Label Proof-of-Concept Study of HTD1801 in Adult Subjects with Primary Biliary Cholangitis (PBC) and an Inadequate Response to Standard Therapy (PRONTO-PBC)

Protocol Number: HTD1801.PCT013

INVESTIGATOR APPROVAL

I confirm that I have read this protocol. I will comply with the protocol, statutory requirements as described in the United States Code of Federal Regulations (CFR) 21 Parts 11, 50, 54, 56, and 312, and local requirements in the countries where the study is performed, the principles of Good Clinical Practice (GCP) in relevant guidance documents from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the ethical principles of the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all study site personnel who participate in the conduct of this clinical study. I will discuss this material with them to ensure they are fully informed regarding the study medication, the conduct of the study, and the obligations of confidentiality.

Principal Investigator Name (Printed) _____ Signature _____

Date _____ Study Center Number _____

Institution Name _____ City, State or Province, Country _____

SPONSOR APPROVAL

ADRIAN M. DI BISCEGLIE _____

Sponsor Name (Printed) Signature

22nd August 2021.

Date

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. PROTOCOL SUMMARY

1.1. Synopsis

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<tr><td colspan="2">Name of sponsor company: HighTide Biopharma Pty. Ltd.</td></tr>
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<tr><td colspan="2">Investigator(s): Multicenter</td></tr>
<tr><td colspan="2">Number of sites: Up to 20</td></tr>
<tr><td>Study periods:
Pre-screening: Up to 28 days
Screening: Up to 28 days
Open-label treatment: 12 weeks
Follow-up: 28 days after last dose of investigational product (IP)</td><td>Phase of development: 2</td></tr>
<tr><td>Objectives</td><td>Endpoints</td></tr>
<tr><td rowspan="2">Primary Objective:
To evaluate the effects of HTD1801 on serum alkaline phosphatase (ALP) in adult subjects with PBC who have experienced an inadequate response to standard therapy.
Inadequate response is defined as ALP ≥1.5 × ULN despite having been on adequate doses of UDCA for at least 6 months.</td><td>Primary Endpoint:
• Percent change in ALP at Week 12 compared to Baseline.</td></tr>
<tr><td>Additional ALP Secondary Endpoints:
• Absolute change in ALP at Week 12 compared to Baseline
• Proportion of subjects who have ≥20% decrease in ALP from Baseline to Week 12
• Proportion of subjects who have ≥40% decrease in ALP from Baseline to Week 12
• The proportion of subjects who normalize ALP at Week 12</td></tr>
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• Change in ALT from Baseline to Week12
• Change in AST from Baseline to Week 12</td></tr>
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<tr><td>To evaluate the effects of HTD1801 on serum markers of inflammation</td><td>• Change in inflammatory serum markers including fibrinogen, CRP, Haptoglobin, ELF and serum immunoglobulins between Baseline and Week 12</td></tr>
</table>

To evaluate the safety and tolerability of HTD1801 over 12 weeks of treatment in adult subjects with PBC	• Change in GLOBE score between Baseline and Week 12 • Change in pruritus as measured by Pruritus visual analog score (VAS) between Baseline and Week 12 • Adverse events and changes in physical examination, vital signs, and clinical laboratory values
To evaluate the pharmacokinetic profile of HTD1801in a subset of subjects participating in this study	Descriptive statistics on plasma concentrations of measured analytes for berberine and UDCA and its conjugates

Study Design: A single arm, 12-week open-label study with follow-up 28 days after last dose of IP. Upon confirmation of eligibility, subjects will be enrolled and will receive HTD1801 1000 mg BID for 12 weeks.

Number of subjects: Up to 30 subjects. If a subject discontinues from the study for any reason other than safety prior to the first post-dose assessment, an additional subject may be enrolled.

Inclusion criteria:

1. Male or female between 18 and 75 years of age, inclusive
2. Have a clinical diagnosis of PBC as confirmed by patient history consistent with the American Association for the Study of Liver Diseases (AASLD) Practice Guideline confirmed by two of the following three criteria:
   a) Biochemical evidence of cholestasis with elevation of ALP activity
   b) Presence of antimitochondrial antibody (AMA)
   c) Histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts if biopsy performed

   Note: historical AMA and liver biopsy data may be used but must be recorded in source documentation.
3. Has been taking a stable, adequate dose (at minimum 13mg/kg/day) of UDCA for at least 6 months, with a serum ALP of ≥1.5 × ULN
4. Has two consecutive values of ALP ≥1.5x ULN (historical and screening values) of which the second ALP value must not be down trending relative to the first ALP value

   a. If the historical ALP value was obtained more than 6 months prior to study start as part of standard of care, a more recent historical value should be obtained as a part of a pre-screening visit. If this more recent value is ≥1.5 × ULN, the subject may be scheduled for full screening as soon as 4 weeks later and a second ALP value should be obtained as part of full screening. Both values must be ≥1.5x ULN.

   b. If the historical ALP value was obtained less than 6 months prior to study start as part of standard of care, the subject may be screened and a second ALP value should be obtained as part of screening. There must be at least a 4-week interval between the ALP values. Both values must be ≥1.5x ULN.

   c. If the screening ALP value is more than ≥30% lower than the historical value obtained as part of standard of care, the subject will not qualify for enrollment but may be re-screened as soon as 4 weeks later. If on re-screening the ALP value continues to be >30% lower, the subject will not be eligible to be in the study. Because there may be

considerable variability in the reference range for ALP obtained for the historical value, the estimation of downward trends of more than 30% should take this into account

5. Be willing to discontinue UDCA the day prior to the start of IP dosing
6. Be willing to discontinue the use of berberine supplements or berberine herbal products the day prior to the start of IP dosing
7. If the subject is taking cholestyramine or other bile acid sequestrant for pruritus, the subject must be on a stable dose and taking it no more than once a day for at least 8 weeks prior to Baseline visit. Must be willing and able to take cholestyramine at least 2 hours before or after study medication
8. Females of child-bearing potential and males participating in the study must either agree to use at least two approved barrier methods of contraception or be completely abstinent from sexual intercourse, if this is their usual and preferred lifestyle, throughout the duration of the study and for three months after stopping study drug. Females who are postmenopausal must have appropriate documentation
9. Be able to understand and sign a written or electronic informed consent form (ICF)

Exclusion criteria:

1. Uncontrolled concomitant autoimmune hepatitis (AIH). Subject should be on no more than 5 mg per day of prednisone (or equivalent dose for other corticosteroids) or no more than 150 mg per day of azathioprine at stable doses and serum ALT should be ≤ 5 × ULN. Use of medications other than prednisone or azathioprine for the treatment of AIH is prohibited (e.g., Mycophenolate). Stable use of immunosuppressives for other indications may be permitted (see below). Enrollment of subjects with controlled AIH will be limited to a total of 5 subjects.
2. Other plausible reasons for elevations in serum alkaline phosphatase such as drug-induced liver injury, concomitant cholestatic liver disease or bone disease.
3. History of alcohol or substance abuse
4. Prior liver transplantation or currently listed for liver transplantation
5. History of chronic viral hepatitis, types B or C
6. Platelet count <150,000/mm^3, albumin <3.0 g/dL, International Normalized Ratio (INR) >1.2, or a history of ascites, or encephalopathy, or history of variceal bleeding
7. Total bilirubin >1.3 mg/dL unless subject has Gilbert's Syndrome. If subject has increased total bilirubin due to Gilbert's Syndrome, then direct bilirubin should be <0.3 mg/dL.
8. Hemoglobin <10 g/dL for males or females
9. Serum TSH level <0.1 or >10 u/mL (subject may be re-screened if hyper- or hypothyroidism has been corrected)
10. Renal impairment with eGFR <60ml/min/1.73 m^2 (CKD stages 3, 4 or 5)
11. Human immunodeficiency virus (HIV)-1 or HIV-2 infection by history
12. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a screening assay will be performed. If serum level is below normal, clinical evaluation and further testing may be needed to confirm a diagnosis of G6PD deficiency.
13. History of malignancy within the past 2 years or ongoing malignancy other than basal cell carcinoma, or resected noninvasive cutaneous squamous cell carcinoma
14. Active, serious infections that require parenteral antibiotic or antifungal therapy within 30 days prior to Screening
15. Major surgical procedure within 30 days of Screening or prior solid organ transplantation
16. Females who are pregnant or breastfeeding
17. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents, and immune-modulating agents (such as interleukins, interferons). Chronic, stable use of immunosuppressive medication may be allowed with medical monitor approval
18. Allergy to the clinical trial material or its components
19. Having received any experimental medications within 28 days prior to Screening

20. Use of bezafibrate or fenofibrate within 28 days prior to first day of IP dosing
21. Use of obeticholic acid (OCA) within 28 days prior to first day of IP dosing
22. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements

Test product, dose, and mode of administration:
HTD1801: 1000 mg administered as tablets twice daily with food

Reference therapy, dose and mode of administration: N/A

Duration of treatment: Up to 12 weeks

Criteria for Evaluation:

Efficacy Evaluation

Efficacy endpoints will be evaluated with descriptive statistics to include 95% confidence intervals. Testing will be used. For the primary endpoint a one sample t-test against a null hypothesis of no change, will be used with a 5% one-sided alpha level. The safety population will include all treated subjects and the efficacy population will include all treated subjects with at least one post dose ALP assessment. Baseline will be assigned to the last available assessment prior to the start of treatment.

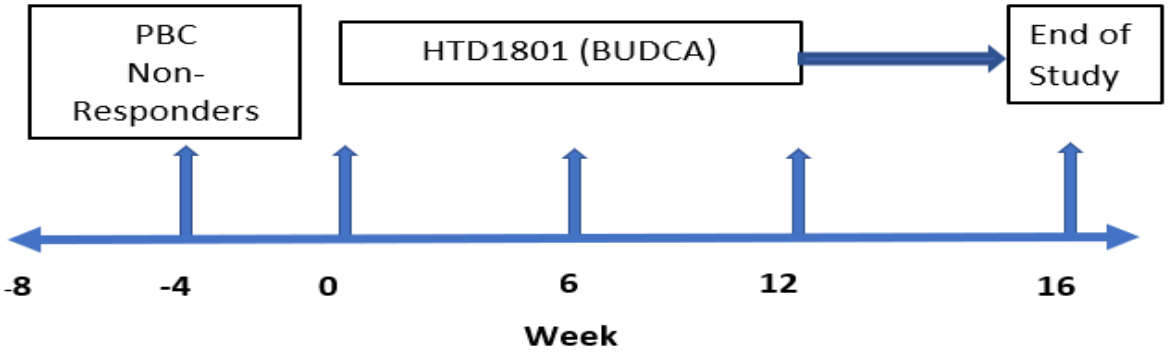
Safety Evaluation

Adverse events and changes in clinical laboratory assessments will be used to evaluate safety and tolerability. Safety data will be summarized using descriptive analysis.

Sample Size:

A sample size of 30 subjects provides ≥90% power for the primary endpoint assuming a mean percent reduction in ALP of 15% and a SD of 25%. Power calculations use a 5% one sided alpha and a t-test.

1.2. Schema



Optional Pre-Screening for ALP	**Screening**	**Baseline Initiate IP Dosing**	**IP Dosing** HTD1801 1000 mg BID					**Follow-Up End of Study**
Day -56 to Day -28	Day -28 to Day -1	Day 0	Week 2 Day 14 ±3 days	Week 4 Day 28 ±3 days	Week 6 Day 42 ±3 days	Week 8 Day 56 ±3 days	Week 12 Day 84 ±3 days	Week 16 Day 112 ±5 days

PK Sampling: -30 minutes prior to dosing, 4 hours ±30 minutes and 8 hours ±30 minutes post-dosing for subset of at least 6 subjects

PK Sampling: -30 minutes prior to dosing, 4 hours ±30 minutes and 8 hours ±30 minutes post-dosing for subset of at least 6 subjects

1.3. Schedule of Activities

Table 1 Schedule of Events

	Optional Pre-screeing	Screening	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk12	ET[h]	Wk 16 Follow-up
Visit Day	**-56 to -28**	**-28 to -1**	**0**	**14**	**28**	**42**	**56**	**84**	**NA**	**+28d (Day 112)**
Procedure / Window		**-**	**-**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		**±5d**
Clinic visit	X	X	X	Xd	X[d]	X	X[d]	X	X[d]	X[i]
Informed consent	X	Xj								
Eligibility criteria		X	X[a]							
Demographics		X								
Medical history		X	X[a]							
Assign subject ID#	X	X								
Dispense study drug			X			X				
Return study drug						X[b]		X[b]	X[b]	
Study discharge									X	X
Complete physical examination		X								
Targeted physical examination [c]			X[c]			X[c]		X[c]	X[c]	X[c]
Vital signs		X	X			X		X	X	X
Weight		X	X			X		X	X	X
Height		X								
BMI (calculated within EDC)		X								
ECG		X						X	X	
Serum chemistry panel including GGT	X	X	X	X[d]	X[d]	X	X[d]	X	X[d]	X[d]
Lipid panel (triglycerides, HDL-c, LDL-c, and total cholesterol)		X[i]	X[i]			X[i]		X[i]	X[i]	
CBC with differential (no smear)		X	X			X		X	X	
INR		X				X		X	X	
Fibrinogen		X	X			X		X	X	

	Optional Pre-screeing	Screening	Baseline	Wk 2	Wk 4	Wk 6	Wk 8	Wk12	ET[h]	Wk 16 Follow-up
Visit Day	**-56 to -28**	**-28 to -1**	**0**	**14**	**28**	**42**	**56**	**84**	**NA**	**+28d (Day 112)**
Procedure / Window		**-**	**-**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		**±5d**
CRP		X	X			X		X	X	
Haptoglobulin		X	X			X		X	X	
ELF		X	X			X		X	X	
G6PD		X								
IgM		X	X			X		X	X	
IgG		X	X			X		X	X	
Bile acid panel[e]			X[e]			X[e]		X[e]	X[e]	
AMA		X								
ANA		X								
TSH		X								
FSH[f]		X[f]								
PK blood draw[g]						X[g]		X[g]		
Urine Pregnancy Test			X[k]					X[k]	X[k]	
GLOBE Score			X[l]			X[l]		X[l]	X[l]	
Pruritus VAS		X	X			X		X	X	
Adverse event monitoring			X[a]	X	X	X	X	X	X	X
Prior and concomitant medications		X	X[a]	X	X	X	X	X	X	X

Abbreviations: AMA = antimitochondrial antibody; ANA = antinuclear antibody; BMI = body mass index; CBC = complete blood count; CRP = C-reactive protein; ECG = electrocardiogram; EDC = electronic data capture; ELF = enhanced liver fibrosis; FSH = follicle stimulating hormone; G6PD = glucose-6-phosphate dehydrogenase; GGT = gamma-glutamyl transferase; HDL-c = high-density lipoprotein cholesterol; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDL-c = low-density lipoprotein cholesterol; PBC = primary biliary cholangitis; TSH = thyroid stimulating hormone; VAS = visual analogue scale

a Confirm continued eligibility
b IP return and reconciliation
c Targeted PE to include assessment of only those findings that were abnormal at Screening/Baseline visit and any new symptoms exhibited or volunteered by subject
d Optional “in-home” blood draw for COVID-19 contingency measures

e Bile Acid Panel only for those subjects for whom a sample was obtained at Baseline
f Female subjects only, To confirm menopausal status
g Drawn -30 minutes prior to dosing at Week 6 and Week 12; drawn 4 hours (±30 minutes) and 8 hours (±30 minutes) post investigational study drug dosing at Week 6 and Week 12
h Subject who ET will be requested to come back 28 days after their last study dose
i Subjects to fast but may have unsweetened, clear coffee, tea or water but no food after supper the evening before
j If consent not obtained prior to optional pre-screening visit
k Only for women of childbearing potential
l GLOBE score calculated by the biostatistician at the completion of the study

2. INTRODUCTION

2.1. Background

2.1.1. Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is a chronic, slowly progressive autoimmune liver disease. PBC mainly affects women (90%) and, typically, is diagnosed between the ages of 35 - 60. It is characterized by inflammation and destruction of small bile ducts, accompanied by fibrosis (excess fibrous connective tissue) and eventually cirrhosis (extensive scarring of the liver). Another key feature is the presence of specific anti-mitochondrial antibodies (AMA) in the blood in over 90% of the patients.

PBC is a relatively rare disease and occurs worldwide. The incidence and prevalence in various countries and regions differ considerably and have been reported to vary from 0.33 to 5.8 and 1.91 to 40.2 cases per 100 000 inhabitants, respectively.

Many PBC patients do not experience any symptom at diagnosis or during the course of the disease and are diagnosed after the finding of abnormal liver tests at screening or testing for other conditions. However, a significant proportion of patients do have symptoms that can markedly influence the quality of life. The most common symptoms are fatigue and itching.

Treatment with ursodeoxycholic acid (UDCA) is standard for PBC and can improve liver function tests and slow the progression of disease. UDCA was first approved in 1997 in the US for the treatment of PBC (URSO 250 and URSO Forte Prescribing Information 2013). In a study of 180 patients with PBC, UDCA at doses of 13 to 15 mg/kg/day was shown to improve liver biochemistry, delay the progression of liver disease, and prevent the need for liver transplantation relative to placebo treatment (Levy 2003, Lindor 1996). The results of another randomized, double-blind, placebo-controlled trial enrolling 103 patients with PBC showed that 13 to 15 mg/kg/day UDCA was associated with a 5-fold lower progression rate from early stage disease to extensive fibrosis or cirrhosis (Corpechot 2000). Up to 40% of PBC patients have an inadequate response to UDCA and may continue to have disease progression. Obeticholic acid (OCALIVA, OCA), a farnesoid X receptor (FXR) agonist, is indicated for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA (OCALIVA Prescribing Information 2020). The addition of OCA to UDCA can significantly improve serum ALP, GGT, ALT and total bilirubin, which are markers of clinical outcome in PBC (Bahar 2018; Hirschfield 2015).

2.1.2. HTD1801

HTD1801 is a novel salt formed between berberine (BBR) and ursodeoxycholic acid (UDCA) with a stoichiometry of 1:1. HTD1801 is currently being developed as an oral treatment for PBC, primary sclerosing cholangitis (PSC), and nonalcoholic steatohepatitis (NASH). HTD1801 is expected to dissociate into BBR salt and UDCA after oral administration. Due to the different mechanisms of the two products, at least an additive, and possibly an additive or synergistic effect may occur when they are administered together in the form of HTD1801. This study will evaluate HTD1801 in adult subjects with PBC by assessing effects of alkaline phosphatase (ALP) over 12 weeks.

Further information on the use of HTD1801 in clinical and nonclinical studies can be found in the Investigator's Brochure.

2.2. Study Rationale

HTD1801 is a salt of ursodeoxycholic acid (UDCA) and berberine (BBR). UDCA has been the mainstay of primary biliary cholangitis (PBC) for many years and has dramatically improved the prognosis of the disease. UDCA is now registered around the world for the first-line treatment of the disease. Unfortunately, around 40 to 50% of PBC patients do not respond to UDCA or do not maintain an adequate response to UDCA. An inadequate response to UDCA is defined as a persistence of a biochemical cholestatic syndrome and is generally expressed as a persistent increase of serum alkaline phosphatase (ALP) above 1.67 times the upper limit of normal for the laboratory performing the analysis. Unfortunately, around 50% of PBC patients who are incomplete responders to UDCA do not respond to the addition of obeticholic acid. In addition, treatment with obeticholic acid may induce or exacerbate pruritus, a symptom frequently affecting PBC patients, and thus may lead to treatment discontinuation. Hence, there is still an unmet medical need in PBC patients.

The addition of BBR to UDCA, as a salt, in HTD1801 could deliver a benefit to PBC patients who are inadequate responders to UDCA alone. While BBR alone has not been studied in PBC, non-clinical data obtained with HTD1801 support studying the drug in PBC. In a rat model of cholestasis and liver inflammation, the bile duct ligation model, HTD1801 was effective in decreasing liver inflammation and necrosis, and improving bile duct health by reducing inflammation in the portal area and controlling bile duct proliferation. In addition, HTD1801 treatment was associated with an improvement in serum markers of cholestasis (ALP and GGT). In this model, UDCA generally gives mixed results and thus the improvement could be rationalized to come from the association of BBR and UDCA in HTD1801.

2.3. Risk/Benefit Assessment

2.3.1. Known Potential Risks

HTD1801 has been evaluated in a clinical study in patients with NASH and type II diabetes. In that study, HTD1801 was well tolerated at 1000 mg BID and 500 mg BID dose levels. The most common treatment-related AEs were gastrointestinal disorders (diarrhea and nausea), which occurred more frequently in the HTD1801 1000 mg BID dose group compared with the 500 mg BID dose group.

2.3.2. Known Potential Benefits

Based on nonclinical and clinical data in other indications with HTD1801, and the known clinical benefits of BBR and UDCA, it is reasonable to expect potential benefit of HTD1801 in subjects with PBC.

2.3.3. Assessment of Potential Risks and Benefits

The known and potential risks anticipated with HTD1801 appear justified by the potential benefits that may be afforded to subjects with PBC.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective: To evaluate the effects of HTD1801 on serum alkaline phosphatase (ALP) in adult subjects with PBC who have experienced an inadequate response to standard therapy. Inadequate response is defined as ALP ≥1.5 × ULN despite having been on adequate doses of UDCA for at least 6 months	**Primary Endpoint:** • Percent change in ALP at Week 12 compared to Baseline. **Additional ALP Secondary Endpoints:** • Absolute change in ALP at Week 12 compared to Baseline • Proportion of subjects who have ≥20% decrease in ALP from Baseline to Week 12 • Proportion of subjects who have ≥40% decrease in ALP from Baseline to Week 12 • The proportion of subjects who normalize ALP at Week 12
Secondary Objectives:	**Secondary Endpoints:**
To evaluate the effects of HTD1801 on serum markers of cholestasis	• Change in total bilirubin from Baseline to Week 12 • Change in serum gamma-glutamyl transferase (GGT) between Baseline and Week 12 • Change in ALT from Baseline to Week12 • Change in AST from Baseline to Week 12
To evaluate the effects of HTD1801 on serum lipids	• Change in serum cholesterol (total and LDL) and triglyceride levels between Baseline and Week 12
To evaluate the effects of HTD1801 on serum markers of inflammation	• Change in inflammatory serum markers including fibrinogen, CRP, Haptoglobin, ELF and serum immunoglobulins between Baseline and Week 12
To evaluate the safety and tolerability of HTD1801 over 12 weeks of treatment in adult subjects with PBC	• Change in GLOBE score between Baseline and Week 12 • Change in pruritus as measured by Pruritus visual analog score (VAS) between Baseline and Week 12 • Adverse events and changes in physical examination, vital signs, and clinical laboratory values
To evaluate the pharmacokinetic profile of HTD1801in a subset of subjects participating in this study	• Descriptive statistics on plasma concentrations of measured analytes for berberine and UDCA and its conjugates

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, multicenter, single arm, 12-week open-label proof-of-concept study of HTD1801 is adult subjects with PBC with an inadequate response to standard therapy. Inadequate response is defined as ALP ≥1.5 × ULN despite having been on adequate doses of UDCA for at least 6 months. Up to 30 subjects may be enrolled at up to 20 participating clinical sites.

Subjects may be pre-screened 28 to 56 days prior to the screening day visit using the central laboratory to confirm that their alkaline phosphatase is ≥1.5 x ULN and then will enter a screening period of up to 28 days prior to initiating therapy. Upon confirmation of eligibility, subjects will be enrolled and will receive HTD1801 1000 mg BID for 12 weeks. Study visits will occur at Day 0, Weeks 2, 4, 6, 8, and 12. A final follow-up visit will occur at Week 16, 4 weeks after the last dose of study drug. The Week 2, 4, and 8 visits may be performed remotely (home visits).

4.2. Scientific Rationale for Study Design

This is a single arm, open-label proof-of-concept study. All subjects will receive active study drug treatment. This study design is appropriate for a proof-of-concept study for an intervention in a new indication for PBC patients where the laboratory markers do not improve spontaneously and over time, are expected to get worse. Hence, seeing improvements, even without a control arm, is sufficient to meet the scientific goal of providing an indication of efficacy while also providing safety data.

4.3. Justification for Dose

The justification for the dose of HTD1801 selected for this study is based on HighTide's experience with this agent in previous clinical trials in other diseases. A Phase 1b/2a study was conducted in subjects with hyperlipidemia and a Phase 2 study was conducted in subjects with NASH. Even though these are different patient populations from the population to be evaluated in study HTD1801.PCT013, the observations from these studies help inform dose selection in PBC.

In the Phase 1b/2a study (study HTD1801.PCT004), in patients with hyperlipidemia, multiple ascending doses of HTD1801 500 mg, 1000 mg and 2000 mg per day were evaluated for up to 28 days. In this study HTD1801 2000 mg per day was effective in lowering serum cholesterol levels by approximately 11% (Di Bisceglie 2020).

In the Phase 2 study in NASH (Study HTD1801.PCT012), two doses of HTD1801 were evaluated – 1000 mg per day and 2000 mg per day both given for 18 weeks. The dose of 2000 mg per day was effective in decreasing liver fat content and improving glycemic control, more so than the 1000 mg per day dose (Harrison et al. 2020).

In this same study, it was found that the relationship between decrease in liver fat content and body weight at baseline revealed no meaningful trends, implying that the pharmacodynamic changes associated with HTD1801 are relatively unaffected by body weight (see Figure 1; Study # HTD1801.PCT012) (Harrison et al. 2020).

The dose of HTD1801 to be used in this study, 1000 mg BID, is therefore expected be sufficient to show a preliminary treatment response in this 12-week study and also be generally well tolerated. HTD1801 has been shown in previous clinical studies, including in subjects with NASH and PSC, to have a favorable safety profile; gastrointestinal (GI) events were the most common adverse event in these studies; in the study in NASH 12% of subjects who received 1000 mg BID administration discontinued study drug due to GI events whereas there were no discontinuations due to these events in the study in PSC.

For the reasons cited above, the dosage of HTD1801 selected for this study (1000mg BID) is considered appropriate for use in the study population.

4.4. End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities, Section 1.3.

The end of the study is defined as the date of completion of the last visit or procedure shown in the Schedule of Activities in the trial globally for the last subject in the study.

The end of enrollment if less than 30 subjects will be a collaborative decision between regulatory and Sponsor entities.

5. STUDY POPULATION

5.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female between 18 and 75 years of age
2. Has a clinical diagnosis of PBC as confirmed by patient history consistent with the American Association for the Study of Liver Diseases (AASLD) Practice Guideline (Lindor 2019) confirmed by two of the following three criteria:
   a. Biochemical evidence of cholestasis with elevation of ALP activity
   b. Presence of antimitochondrial antibody (AMA)
   c. Histopathologic evidence of nonsuppurative cholangitis and destruction of small or medium-sized bile ducts if biopsy performed

   Note: historical AMA and liver biopsy data may be used, but must be recorded in source documentation.
3. Has been taking a stable, adequate dose (at minimum 13 mg/kg/day) of UDCA for at least 6 months with a serum ALP of ≥1.5 × ULN.
4. Has two consecutive values of ALP ≥1.5 × ULN (historical and screening values) of which the second ALP value must not be down trending relative to the first ALP value
   a. If the historical ALP value was obtained more than 6 months prior to study start as part of standard of care, a more recent historical value should be obtained either using the local laboratory or alternatively, a chemistry sample can be submitted to the central laboratory as a part of an optional pre-screening visit. If this more recent value is ≥1.5 × ULN, the subject may be scheduled for a full screening visit as soon as 4 weeks later and a second ALP value should be obtained as part of full screening. Both values must be ≥1.5 x ULN.
   b. If the historical ALP value was obtained less than 6 months prior to study start as part of standard of care, the subject may be screened and a second ALP value should be obtained as part of screening. There must be at least a 4-week interval between ALP values. Both values must be ≥1.5 x ULN.
   c. If the screening ALP value is more than ≥30% lower than the historical value obtained as part of standard of care, the subject will not qualify for enrollment but may be re-screened as soon as 4 weeks later. If on re-screening the ALP value continues to be >30% lower, the subject will not be included in the study. Because there may be considerable variability in the reference range for ALP obtained for the historical value, the estimation of downward trends of more than 30% should take this into account.
5. Be willing to discontinue UDCA the day prior to the start of IP dosing.
6. Be willing to discontinue the use of berberine supplements or berberine herbal products the day prior to the start of IP dosing

7. If the subject is taking cholestyramine or other bile acid sequestrant for pruritus, the subject must be on a stable dose and taking it no more than once a day for at least 8 weeks prior to Baseline visit. Must be willing and able to take cholestyramine at least 2 hours before or after study medication.
8. Females of child-bearing potential and males participating in the study must either agree to use at least two approved barrier methods of contraception or be completely abstinent from sexual intercourse, if this is their usual and preferred lifestyle, throughout the duration of the study and for three months after stopping study drug. Females who are postmenopausal must have appropriate documentation
9. Be able to understand and sign a written or electronic informed consent form (ICF)

5.2. Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in the study.

1. Uncontrolled concomitant autoimmune hepatitis (AIH). Subject should be on no more than 5 mg per day of prednisone (or equivalent dose for other corticosteroids) or no more than 150 mg per day of azathioprine at stable doses and serum ALT should be ≤5 × ULN. Use of medications other than prednisone or azathioprine for the treatment of AIH is prohibited (e.g., Mycophenolate). Stable use of immunosuppressives for other indications may be permitted (see below). Enrollment of subjects with controlled AIH will be limited to a total of 5 subjects.
2. Other plausible reasons for elevations in serum alkaline phosphatase such as drug-induced liver injury, concomitant cholestatic liver disease or bone disease.
3. History of alcohol or substance abuse
4. Prior liver transplantation or currently listed for liver transplantation
5. Presence of chronic viral hepatitis, types B or C.
6. Platelet count <150,000/mm^3, albumin <3.0 g/dL, International Normalized Ratio (INR) >1.2, or a history of ascites, or encephalopathy, or history of esophageal variceal bleeding
7. Total bilirubin >1.3 mg/dL unless subject has Gilbert's Syndrome. If subject has increased total bilirubin due to Gilbert's Syndrome, then direct bilirubin should be <0.3 mg/dL.
8. Hemoglobin <10 g/dL for males or females
9. Serum TSH level <0.1 or >10 u/mL (subject may be re-screened if hyper- or hypothyroidism has been corrected)
10. Renal impairment with eGFR <60ml/min/1.73 m^2 (CKD stages 3, 4 or 5)
11. Human immunodeficiency virus (HIV)-1 or HIV-2 infection by history
12. Glucose-6-phosphate dehydrogenase (G6PD) deficiency. A screening assay will be performed. If serum level is below normal, clinical evaluation and further testing may be needed to confirm a diagnosis of G6PD deficiency.

13. History of malignancy within the past 2 years or ongoing malignancy other than basal cell carcinoma, or resected noninvasive cutaneous squamous cell carcinoma
14. Active, serious infections that require parenteral antibiotic or antifungal therapy within 30 days prior to Screening
15. Major surgical procedure within 30 days of Screening or prior solid organ transplantation
16. Females who are pregnant or breastfeeding
17. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents, and immune-modulating agents (such as interleukins, interferons). Chronic, stable use of immunosuppressive medications may be allowed with medical monitor approval
18. Allergy to the clinical trial material or its components
19. Having received any experimental medications within 28 days prior to Screening
20. Use of bezafibrate or fenofibrate within 28 days prior to first day of IP dosing
21. Use of obeticholic acid (OCA) within 28 days prior to first day of IP dosing
22. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements

5.3. Screen Failures

Potential subjects who do not meet all eligibility criteria at Screening will be allowed to rescreen once if the Investigator believes that there has been a change in eligibility status. If a potential subject fails to meet eligibility criteria upon rescreen, he/she will remain ineligible for the study.

6. STUDY INTERVENTION

6.1. Study Intervention Administration

6.1.1. Study Intervention Description

The HTD1801 drug substance, berberine ursodeoxycholate, is the salt formed between BBR and UDCA with a stoichiometry of 1:1. The HTD1801 drug product is a film coated tablet containing 250 mg of berberine ursodeoxycholate.

6.1.2. Dosing and Administration

HTD1801 tablets (1000 mg dose) are administered twice daily (BID) with food. Subjects are instructed to take the entire contents of 1 pouch of study drug each morning and each evening with water and food (e.g., meal or snack). Each pouch will contain 4 identical white tablets. Subjects should retain the empty pouches and return them to the investigational site at the Week 6 study visit and Week 12 or Early Termination visit should it occur, along with any unused study drug. Returned unused study drug must not be re dispensed to subjects.

6.1.3. Dose Modification

In the event of gastrointestinal (GI) discomfort as outlined in Section 9.3.8 at the starting dose of 1000 mg BID (4 tablets in the morning after a meal and 4 tablets in the evening after a meal), dose reduction is allowed per the following guidelines:

- For GI symptoms that are difficult for the subject to tolerate, decrease dose to 1500 mg per day (3 tablets in the morning after a meal and 3 tablets in the evening after a meal) for 1 week. If symptoms improve, subject should stay on that dose and not attempt to go back up to full dose.
- If symptoms persist after 1 week at the lower 1500 mg per day dose, decrease dose to 1000 mg per day (2 tablets in the morning after a meal and 2 tablets in the evening after a meal) for 1 week. If symptoms improve, subject should stay on that dose and not attempt to go back up to full dose.
- If symptoms persist after 1 week at the lower 1000 mg per day dose and are intolerable for the subject at this point, study drug is to be discontinued but the subject should continue to be followed as per the Schedule of Activities.

Subjects who will have their dose of study drug decreased will be monitored closely with serum ALP, aminotransferases and bilirubin levels being measured every 2 to 4 weeks. Elevations in ALP or bilirubin will be promptly recognized by the site PI and by the medical monitor because this is an open label study. If ALP levels after having been lowered on initial treatment go back up to baseline or higher on two subsequent occasions (baseline being the average of the historical value and the value at screening)., the subject will be deemed to be a treatment failure and will discontinue investigational study drug (see Section 7.3).

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Acquisition and Accountability

HTD1801 250 mg tablets will be supplied by HighTide to each investigational site. The Investigator will be fully responsible for the security, accessibility, and storage of the study drugs while they are at the investigational site. The Investigator is also responsible for the education of site staff in the correct administration of the study drugs and must ensure that appropriate study drug accountability records are maintained.

The PI and study personnel are responsible for ensuring full investigational product accountability.

6.2.2. Formulation, Appearance, Packaging, and Labeling

The HTD1801 drug product is a white to off-white film-coated tablet containing 250 mg of HTD1801.

Inactive excipients include a silicified microcrystalline cellulose (SMCC90), sodium carboxymethyl starch, and magnesium stearate. The tablets are coated with Opadry® immediate release film (product grade: 03A18375), resulting in an average gain of 15 mg/tablet. The qualities of all excipients are consistent with both the Chinese and US Pharmacopeia standards.

HTD1801 tablets are packaged into polyethylene terephthalate/aluminum foil/polyethylene (PET/AL/PE) pouches. Each pouch will contain 4 HTD1801 250 mg tablets and be affixed with a single-panel label that will describe the following information at a minimum: study drug, dose, kit number, Sponsor name, instructions for storage between 36°F and 46°F (2°C and 8°C), and includes the statements “Caution: New Drug - Limited by United States law to investigational use” and “Keep out of reach of children.”

An adequate supply of pouches will be placed into kits packaged for weekly use, and each subject will receive the appropriate number of kits to provide enough supplies until the Week 6 study visit to the investigational site. Each kit will bear a label describing the following information at a minimum: kit number, Sponsor name, instructions for storage between 36°F and 46°F (2°C and 8°C), and includes the statements “Caution: New Drug - Limited by United States law to investigational use” and “Keep out of reach of children.”

6.2.3. Product Storage and Stability

HTD1801 tablets should be stored at 2-8ºC in the original container and protected from moisture and light.

6.3. Study Intervention Compliance

At applicable clinical visits during the study, subjects will be queried about their compliance with taking their assigned study drug as instructed. The number of full and empty study drug pouches will be captured on the eCRF.

6.4. Concomitant Therapy

6.4.1. Permitted Concomitant Medications

The use of permitted concomitant medications may continue during the study at the same dosage strength and frequency.

For subject taking cholestyramine or other bile acid sequestrant for pruritus, must be on a stable dose no more than once a day for at least 8 weeks prior to Baseline visit. Must be willing and able to take cholestyramine at least 2 hours before or after study medication.

6.4.2. Prohibited Concomitant Medications

6.4.2.1. Prohibited medications that are active against PBC

Use of the following medications, active against PBC, will be prohibited during the study from Baseline through 28 days after completion:

UDCA

Obeticholic acid

Bezafibrate

Fenofibrate

It is important to emphasize that subjects will be counseled before starting investigational drug and at each visit not to take both UDCA and/or berberine together with HTD1801, as HTD1801 contains both UDCA and berberine.

6.4.2.2. Prohibited medications for the treatment of AIH

Use of medications for the treatment of AIH other than prednisone or azathioprine is prohibited (e.g., Mycophenolate). Stable use of immunosuppressives for other indications may be permitted (see above).

6.4.2.3. Prohibited medications with potential for drug-drug interaction

In addition, certain concomitant medications have been identified for exclusion from this proof-of-concept study and are not to be taken at any time during the entire study (i.e., from Screening through Follow-Up). These exclusions are primarily due to the potential drug interaction profile of the BBR component of HTD1801. Table 2 lists medications known to be strong inhibitors of P glycoprotein (P-gp), CYP3A4, and CYP2D6; strong inducers of CYP3A4, as well as P-gp substrates with a narrow therapeutic index, and that are prohibited from concomitant use during this study.

Supplements with potential for drug-drug interaction should be discussed with the medical monitor prior to enrolling a subject.

Table 2: Prohibited Medications with potential for drug-drug interaction

Single Agents:

P-glycoprotein	CYP3A4		CYP2D6
Clarithromycin	Clarithromycin	Ritonavir	bupropion
Erythromycin	Telithromycin	Saquinavir	fluoxetine
Amiodarone	Troleandomycin	Telaprevir	fluvoxamine
Digitalis	Nefazodone	Tipranavir	paroxetine
Dronedarone	St. John's wort	chloramphenicol	Quinidine
Carvedilol	Itraconazole	Rifampin	Terbinafine
Propafenone	Ketoconazole	Cobicistat	
Quinidine	Posaconazole	grapefruit juice	
Ranolazine	Voriconazole	conivaptan	
Verapamil	Atazanavir	Diltiazem	
Sildenafil	Boceprevir	Idelalisib	
Itraconazole	Darunavir	enzalutamide	
Ketoconazole	Indinavir	Mitotane	
Ritonavir	Lopinavir	carbamazepine	
Saquinavir	Nelfinavir	Phenytoin	
Telaprevir			
Lapatinib			

Combination Agents:

P-glycoprotein	CYP3A4
lopinavir and ritonavir	danoprevir and ritonavir
saquinavir and ritonavir	elvitegravir and ritonavir
tipranavir and ritonavir	indinavir and ritonavir
	lopinavir and ritonavir
	paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
	saquinavir and ritonavir
	tipranavir and ritonavir

Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (Tables 2-2, 2-3, 3-2, 3-3, and 5-2)

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Decrease in dose of study drug

Subjects who have their dose of study drug decreased will be monitored closely with serum alkaline phosphatase, aminotransferases and bilirubin levels being measured every 2 to 4 weeks. Elevations in ALP or bilirubin will be promptly recognized by the site PI and by the medical monitor because this is an open label study. If subjects are deemed to be treatment failures when their dose of study drug is decreased, study drug will be discontinued (see Section 7.2).

7.2. Discontinuation of Study Intervention

HTD1801 treatment must be discontinued for a subject if any of the following criteria are met.

- Adverse event that may jeopardize subject's safety
- Grade 3 and above adverse events (AEs) for which the causality is considered as related to investigational agent
- Discontinuation due to drug-induced liver injury (refer to Section 10)
- Request by the subject
- Pregnancy

For subjects who discontinue investigational study drug, an Early Termination Visit should be conducted at the time the investigational study drug is discontinued (see Section 7.3). Subjects who terminate from the study prior to Study Visit Week 12 will be requested to return to the clinic 28 days **after the date of last dose** of investigational study drug and complete the equivalent of the Week 16 follow up visit assessments. If necessary, arrangements can be made with the site and the subject to conduct the visit virtually and make use of a local laboratory for the study required Study Visit Week 16 lab tests.

7.3. Participant Discontinuation/Withdrawal from the Study

Subjects may be discontinued from the study for any of the following reasons:

- Noncompliance
  - Failure to receive study medication or treatment
  - Failure to comply with protocol requirements
  - Unauthorized, subject-initiated changes in dosing regimen
- Withdrawal of consent
  - Any subject who withdraws consent for any reason at any time during the study will be discontinued from the study, and the reason(s) will be documented on the appropriate eCRF page.
- Lost to Follow-Up

- For subjects who cannot be contacted for either a return for a scheduled clinic visit or for follow-up assessments as described, and who may be considered "lost to follow-up," at least 3 documented attempts should be made to establish contact with and to instruct the subject on how to complete study procedures. In the final attempt to contact the subject, a letter should be sent by certified mail to the subject's last known address

- Adverse Events
  - Study drug will be discontinued in an individual subject if the subject experiences a grade 3 and above adverse event (AE) for which the causality is considered as related to investigational study drug

- Treatment Failure
  - If any subject fails treatment after having their dose of HTD1801 reduced, their participation in the study will be ended and they will be allowed to resume their pre-study treatment for PBC. A subject will be deemed to have failed treatment if serum ALP, after having been lowered on initial treatment, returns to baseline or higher on two subsequent occasions (baseline being the average of the historical value and the value at screening).

7.4. Study Stopping Criteria

If there is one death (grade 5 AE) or two subjects meeting the same grade 4 AE (life threatening or disabling AE), or three subjects meeting the same grade 3 AE (severe AE), the trial will be paused and the AEs assessed for causality. The event data will be submitted to the FDA with a request to resume conduct of the trial.

8. STUDY PROCEDURES AND EVALUATIONS

Study procedures are summarized across all scheduled study visits as indicated in the Study Schema (Section 1.2) and Table 1 Schedule of Activities (Section 1.3). Unscheduled visits may also occur at any time if medically warranted. Study related assessments performed at all visits will be recorded in the eCRF.

Refer to Section 11 for COVID-19 contingency measures for Study Visit Week 2, 4, 8, 16 and ET in case a subject is unable or unwilling to participate in an on-site visit due to the COVID-19 pandemic.

8.1. Pre-screening (Days -56 to -28) ALP

Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. If the historical ALP that was obtained as part of standard of care is not ≥1.5 x ULN or is not within 6 months of the screening visit, a pre-screening visit must be conducted in order to collect a chemistry lab sample to determine the ALP value using the central laboratory. Informed consent needs to be obtained from the subject before proceeding with any study-specific procedures. The pre-screening ALP sample through the central laboratory needs to be obtained at least 28 days prior to full screening visit.

- Informed consent
- Assign subject ID#
- Chemistry sample for alkaline phosphatase

8.2. Screening (Days -28 to -1)

Screening procedures must be completed within 28 days prior to the Baseline visit and can be performed across multiple days during this period. Screening clinical laboratory tests may be repeated once during Screening if the Investigator believes the results to be erroneous. In the event that Screening tests are repeated, the most current results will be used to determine eligibility. If screening procedures are completed and subject eligibility is confirmed, the full 28-day screening period may not be necessary.

During Screening, the following procedures must be conducted and assessments obtained. The information will be collected in the investigational site's standard source documents or in source document templates provided by the Sponsor.

- Informed consent if not obtained at pre-screening visit
- Confirm eligibility criteria
- Demographic information
- Medical history
- Assign subject ID # if not obtained at pre-screening visit
- Complete physical examination
- Vital signs
- Weight, height
- Electrocardiogram, 12 lead (ECG)

- Serum chemistry panel including GGT, Lipid panel -– fasting, unsweetened clear coffee, tea or water permitted but no food after supper the evening before
- Complete blood count (CBC) with differential (no smear)
- INR
- Fibrinogen
- CRP
- Haptoglobulin
- ELF
- G6PD
- IgM
- IgG
- AMA
- ANA
- TSH
- FSH (if needed to confirm menopausal status)
- Pruritus VAS
- Prior and concomitant medications

Subjects will be instructed to stop all prohibited medications (see Section 6.4) prior to beginning Baseline procedures. In particular, subjects will be cautioned against the use of UDCA until their participation in this study is complete.

NOTE: If the screening ALP value is more than ≥30% lower than the historical value obtained as part of standard of care, the subject will not qualify for enrollment but may be re-screened as soon as 4 weeks later. If on re-screening the ALP value continues to be >30% lower, the subject will not be included in the study.

8.3. Baseline/Day 0

Potential subjects who have successfully completed all of the Screening procedures and have met all the eligibility criteria (see Sections 5.1 and 5.2) will be eligible for enrollment in the study. Subjects will undergo the following Baseline procedures and assessments prior to the first dose of study drug:

- Confirmation of continued eligibility
- Update of medical history information
- Targeted physical examination (to include assessment of only findings that were abnormal at Screening/Baseline visit and any new symptoms exhibited or volunteered by subject)
- Vital signs
- Weight
- Serum chemistry panel including GGT

- Lipid panel -– fasting, unsweetened clear coffee, tea or water permitted but no food after supper the evening before
- CBC with differential
- Fibrinogen
- CRP
- Haptoglobin
- ELF
- IGM
- IgG
- Bile acid panel
- Urine pregnancy test for women of childbearing potential
- GLOBE Score (calculated by biostatistical programming based upon age, total bilirubin, alkaline phosphatase, albumin and platelet count)
- Pruritus VAS
- Adverse event monitoring
- Concomitant medications
- Dispense study drug

8.4. Week 2 and Week 4 Visits (±3 days)

Week 2 and Week 4 visits are conducted as in-clinic visits or optional in-home visits. The following procedures and assessments will be conducted at these visits:

- Serum chemistry panel including GGT
- Adverse event monitoring
- Concomitant medications

Refer to Section 11 for COVID-19 contingency measures for Study Visits Week 2 and Week 4 in case a subject is unable or unwilling to participate in an on-site visit due to the COVID-19 pandemic.

8.5. Week 6 Visit (±3 days)

The following procedures and assessments will be performed during the Week 6 clinic visit:

- Targeted physical examination (to include assessment of only findings that were abnormal at Screening/Baseline visit and any new symptoms exhibited or volunteered by subject)
- Vital signs
- Weight
- Serum chemistry panel including GGT
- Lipid panel - fasting, unsweetened clear coffee, tea or water permitted but no food after supper the evening before

- CBC with differential
- INR
- Fibrinogen
- CRP
- Haptoglobin
- ELF
- IGM
- IgG
- Bile acid panel
- PK blood draw for at least 6 subjects who consent to participate in the PK sub-study
    - PK lab draw at -30 minutes prior to investigational study drug dosing
    - PK lab draw at ±30 minutes 4 hours post investigational study drug dosing
    - PK lab draw at ±30 minutes 8 hours post investigational study drug dosing
- GLOBE Score (calculated by biostatistical programming based upon age, total bilirubin, alkaline phosphatase, albumin and platelet count)
- Pruritus VAS
- Adverse event monitoring
- Concomitant medications
- Return study drug/reconciliation
- Dispense study drug

8.6. Week 8 Visit (±3 days)

The Week 8 visit is conducted as an in-clinic visit or optional in-home lab visit. The following procedures and assessments will be conducted at this visit:

- Serum chemistry panel including GGT
- Adverse event monitoring
- Concomitant medications

Refer to Section 11 for COVID-19 contingency measures for Study Visit Week 8 in case a subject is unable or unwilling to participate in an on-site visit due to the COVID-19 pandemic.

8.7. Week 12 Visit (±3 days)

The following procedures and assessments will be performed during the Week 12 clinic visit:

- Targeted physical examination (to include assessment of only findings that were abnormal at Screening/Baseline visit and any new symptoms exhibited or volunteered by subject)
- Vital signs
- Weight
- ECG

- Serum chemistry panel including GGT
- Lipid panel - fasting, unsweetened clear coffee, tea or water permitted but no food after supper the evening before
- CBC with differential
- INR
- Fibrinogen
- CRP
- Haptoglobin
- ELF
- IGM
- IgG
- Bile acid panel
- PK blood draw for at least 6 subjects who consent to participate in the PK sub-study
    - PK lab draw at -30 minutes prior to investigational study drug dosing
    - PK lab draw at ±30 minutes 4 hours post investigational study drug dosing
    - PK lab draw at ±30 minutes 8 hours post investigational study drug dosing
- Urine pregnancy test for women of childbearing potential
- GLOBE Score (calculated by biostatistical programming based upon age, total bilirubin, alkaline phosphatase, albumin and platelet count)
- Pruritus VAS
- Adverse event monitoring
- Concomitant medications
- Return study drug/reconciliation

8.8. Week 16 Visit (±5 days)

The final study visit will occur 28 days after the last dose of study drug at a Week 16 follow-up visit. The Week 16 visit is conducted as an in-clinic visit or optional in-home lab visit. The following procedures and assessments will be conducted at this visit:

- Study discharge
- Targeted physical examination (to include assessment of only findings that were abnormal at Screening/Baseline visit and any new symptoms exhibited or volunteered by subject)
- Vital signs
- Weight

  Serum chemistry panel including GGT
- Adverse event monitoring
- Concomitant medications

Refer to Section 11 for COVID-19 contingency measures for Study Visit Week 16 in case a subject is unable or unwilling to participate in an on-site visit due to the COVID-19 pandemic.

8.9. Early Termination Visit

In the event of early termination from the study, the subject should return to the clinic for the following end of study assessments but may be conducted as an in-home lab visit by a nurse if the subject is unwilling or unable to attend the visit in person due to the COVID-19 pandemic:

- Study discharge
- Targeted physical examination (to include assessment of only findings that were abnormal at Screening/Baseline visit and any new symptoms exhibited or volunteered by subject)
- Vital signs
- Weight
- ECG
- Serum chemistry panel including GGT
- Lipid panel
- CBC with differential
- INR
- Fibrinogen
- CRP
- Haptoglobin
- ELF
- IGM
- IgG
- Bile acid panel
- Urine pregnancy test for women of childbearing potential
- GLOBE Score (calculated by biostatistical programming based upon age, total bilirubin, alkaline phosphatase, albumin and platelet count)
- Pruritus VAS
- Adverse event monitoring
- Concomitant medications
- Return study drug/reconciliation

Subjects who terminate from the study prior to Study Visit Week 12 will be requested to return to the clinic 28 days **after the date of last dose** of investigational study drug and complete the equivalent of the Week 16 follow up visit assessments. This final study visit is conducted as an in-clinic visit or optional in-home lab visit.

Refer to Section 11 for COVID-19 contingency measures for Early Termination Visit in case a subject is unable or unwilling to participate in an on-site visit dur to the COVID-19 pandemic.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. Efficacy Assessments

9.1.1. Serum Alkaline Phosphatase Endpoints

The ALP endpoints including the primary endpoint are based upon laboratory results. Results will be assigned to time points based upon the timing of the sample. Baseline will be the last available ALP result available prior to treatment with HTD1801 and change from baseline and percent change will be based upon this baseline value and the value as the respective timepoint. The binary ≥20% and ≥40% decrease endpoints will be based upon the percent change from baseline measure (did or did not have a percent change of this size). The normalization of ALP endpoint will be based upon the result and the associated normal range provided by the laboratory.

9.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are each based upon laboratory results and the change from baseline of these results. As with the ALP endpoint baseline will be the last available pre-treatment result, change from baseline will be based upon this baseline result and the result at the timepoints. Results will be assigned to timepoints based the timing of the result.

9.2. Safety and Other Assessments

9.2.1. Demographics and Medical History

The Investigator or qualified designee will obtain demographic data, medical history, and medication history for each potential subject at Screening. Demographic data will include, at a minimum, the subject's age and/or date of birth, sex, race, and ethnicity. Medical and medication history will include relevant medical conditions and treatments.

9.2.2. Adverse Events

Adverse events will be collected from the time at which the potential subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study until at least 30 days after discontinuing the study drug. General and non-leading questions such as "How are you feeling?" should be asked when assessing the occurrence of AEs. The definition, reporting, and recording requirements for AEs are described in Section 9.3.

9.2.3. Physical Examinations

Physical examinations must be performed at investigational sites by medically qualified individuals according to local requirements. Abnormal physical examination findings that the Investigator considers clinically significant are to be reported as AEs if they began after the start of treatment and as medical history if they were present prior to treatment.

The comprehensive physical examination will include the assessment of the following: skin; head, neck, eyes, ears, nose, throat; upper and lower extremities; chest and lungs; abdomen; cardiovascular system; and a brief neurological examination. The targeted physical examination

will be a symptom-driven assessment of body systems or organs as indicated by AEs or other findings.

9.2.4. Vital Signs, Height, and Weight

Vital sign measurements must be performed at investigational sites by medically qualified individuals according to local requirements. Measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken in a recumbent, semi recumbent, or sitting position after 5 minutes of rest. Height (at Screening only) and weight will also be performed. Abnormal findings seen after the start of treatment that the Investigator considers clinically significant are to be reported as AEs.

9.2.5. Electrocardiograms

Twelve-lead ECGs will be performed at the investigational site with the subject in a recumbent or semi-recumbent position after 5 minutes of rest. Local institutional standards for QT interval corrections should be utilized. Interpretation of ECG results for the ongoing assessment of safety will be performed by the Investigator or qualified designee during the scheduled visit. Abnormal ECG readings seen after the start of treatment are to be reported as AEs only if they are considered clinically significant by the Investigator. Additionally, the Investigator should consult the Medical Monitor, when possible, for any abnormal, clinically significant ECG findings that may result in a change to the subject's treatment or management.

9.2.6. Safety Related Laboratory Assessments

A central laboratory will be utilized to perform safety related clinical laboratory assessments as specified in the Schedule of Activities Table 1 and as described below in Table 3. Samples for laboratory assessments performed at Baseline must be collected prior to study drug dosing. The Investigator or qualified designee must review the results of all central laboratory testing to assess subject eligibility at Screening and Baseline, as well as continued study participation for the duration of the study. Procedures for sample collection and handling will be detailed in the central laboratory manual and/or Study Procedures Manual (SPM).

Table 3 Laboratory Analytes

Serum Chemistry	Hematology	Lipids	Coagulation
Comprehensive metabolic panel: • Albumin • ALP • ALT • AST • Bicarbonate • Bilirubin, total • Bilirubin, direct • Blood urea nitrogen (BUN) • Calcium • Chloride • Creatinine • eGFR (calculated) • Creatine kinase • GGT • Glucose • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Sodium • Total protein • Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count • Reticulocyte count White blood cell count differential, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Endocrinology: TSH	Total cholesterol LDL-c HDL-c Triglycerides	INR **Other** Fibrinogen CRP Haptoglobin ELF G6PD IgG IgM Bile acids panel AMA ANA Serum and urine pregnancy tests FSH test

9.2.7. GLOBE Score

The GLOBE score is a validated risk assessment tool, able to accurately stratify PBC patients to high and low risk for future adverse events (Lammers 2015). See Appendix A and https://www.globalpbc.com/globe for details on calculating the GLOBE score. While the variables that are used to calculate the GLOBE score are collected as part of the study assessments, actual calculation of the GLOBE score will be completed by biostatistical programming.

Although the GLOBE score calculation is a validated tool for subjects who have been on UDCA therapy for at least 12 months, for the purpose of this study, biostatistics will program a listing that separates subjects by duration of UDCA exposure, i.e., subjects who have been on UDCA for ≥12 months and subjects who have been on UDCA at least 6 months but <12 months.

9.2.8. Pruritus VAS

Subjects will complete an analogue rating scale at the indicated timepoints to describe their severity of pruritus over the last 24 hours prior to their clinic visit (see Appendix B).

9.2.9. Pharmacokinetic (PK) sub-study

At least 6 subjects will be asked to participate in a PK sub-study to evaluate the plasma concentrations of UDCA and berberine. Subjects who consent to participate in this sub-study will receive their dose of study drug in clinic and then provide one pre-dose (-30 minutes prior to dosing) and 2 post-dose samples at 4 hours±30 minutes and at 8 hours±30 minutes at Study Visits Weeks 6 and 12.

9.3. Adverse Events and Serious Adverse Events

9.3.1. Definition of Adverse Event (AE)

The following definition of an AE will be used for this study: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product, regardless of whether it is considered to be related to the investigational product.

The following are examples of AEs:

- Significant or unexpected worsening or exacerbation of the indication under study.
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.

Overdose should not be reported as an AE or serious adverse event (SAE), but rather the symptoms resulting from the overdose should be reported as such.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g., endoscopy, appendectomy). The medical condition that led to the procedure as the AE should be reported.
- Situations that are unwanted by the subject but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital.
- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall.

- Expected progression of the disease being studied, including signs or symptoms of the disease, unless progression is more severe than expected for the subject's condition.

Adverse events may include post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive procedures, modification of the subject's previous therapeutic regimen).

Adverse events should be captured even if they occur during periods without drug treatment, post-treatment periods, known placebo treatment, or in a reference or control group receiving drug or nondrug therapy.

The Investigator is responsible for all AE assessments. The Investigator and investigational site staff will note all AEs mentioned by the subject at Screening, Baseline and during study drug administration. All clinical complaints volunteered by or elicited from the subject during the study will be recorded on the appropriate page of the eCRF for the study period indicated. The subject will receive appropriate treatment and medical supervision for any AE that occurs.

All AEs judged to be clinically significant, including clinically significant laboratory abnormalities, will be followed until resolution. All AEs will be summarized in the clinical study report and the annual report or more frequently if requested by the regulatory agency. Serious adverse events require special reporting in addition to documentation in the eCRF as described in Section 9.3.6.

The severity of adverse events will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf)

9.3.2. Definition of Serious Adverse Event (SAE)

In this study, an SAE is defined as an AE that meets any of the following criteria:

- Results in death.
- Is life-threatening. The term life-threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event. The term life-threatening does not refer to an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or a prolongation of an existing hospitalization. In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs, but not necessarily SAEs. A medical occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatments of a preexisting condition that did not worsen from its original Baseline level is not considered an SAE.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. This does not include AEs of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- A congenital anomaly or birth defect. This refers to the offspring of a study subject.
- Any other important medical event. Medical or scientific judgment should be exercised when deciding whether reporting is appropriate for other important medical events that may not result in death, be life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or in the development of drug dependency or drug abuse.

An SAE requires additional detailed reports and follow-up. The content of these detailed reports must address the Investigator's estimate of causality. The Medical Monitor will review the SAE to determine if it is an expected SAE (i.e., whether or not the SAE is identified in nature, severity, and frequency in the Investigator's Brochure).

9.3.3. Classification of an Adverse Event

9.3.3.1. Severity of Event

The Investigator will assess the severity for each AE and SAE reported during the study on the basis of his or her clinical judgment. Table 4 shows an overview of the severity classification as outlined in CTACE version 5.0. For the purposes of assigning severity of each AE recorded in the source documentation and subsequently, in the eCRF, investigators are encouraged to refer to CTCAE v 5.0 for a more detailed description of any specific AE that may occur.

Table 4 Classification of Adverse Events (AEs) by Severity

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

[a] From Common Terminology Criteria for Adverse Events, Version 5.0

Any AE that changes in severity or grade during a single occurrence of an AE will be recorded in the eCRF at the highest level experienced by the subject.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an AE (such as mild, moderate, or severe myocardial infarction). However, an AE itself may be of relatively minor medical significance, such as a severe headache. Both AEs and SAEs can be assessed as severe. An AE is considered serious when it meets one of the predefined outcomes described in Section 9.3.2.

9.3.3.2. Relationship to Study Intervention

The Investigator must estimate the relationship between the investigational product and the occurrence of each AE or SAE by using his or her best clinical judgment. Elements to consider for this estimate include the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the investigational product. The Investigator will also consult the Investigator's Brochure or product label for marketed products in estimating the relationship.

Because of reporting timelines, the Investigator might have minimal information to include in the initial SAE report. However, the Investigator must always make an assessment of causality for every SAE before the transmission of the SAE report. The Investigator may change his or her opinion of the causality in light of follow-up information, with subsequent amendment of the SAE report. Causality assessment is a criterion used to determine regulatory reporting requirements and should not be left blank on the eCRF. The same applies to AEs that are to be processed as SAEs.

Table 5 provides some definitions to use in the assessment.

Table 5 Assessment of Causality of AEs

Term	Definition
Possibly related	The AE *may be related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention.
Unrelated (or not related)	The AE is *clearly not* related to the investigational agent(s) or intervention: the AE has no temporal relationship to the administration of the investigational agent(s) or research intervention, and follows no known or suspected pattern of response, and an alternative cause is present.

9.3.3.3. Expectedness

An expected AE is one that is consistent with the known risk information described in the product label (if applicable) or the current Investigator's Brochure. The expectedness of an SAE will be assessed by the Medical Monitor and Sponsor on receipt of the initial SAE report.

9.3.4. Time Period and Frequency for Event Assessment and Follow-Up

AEs will be recorded starting after Screening and at every visit through the Week 16 Follow-Up Visit.

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor about the subject's condition. All AEs and SAEs will be followed until the occurrence of one of the following:

- The condition resolves.
- The AE or SAE is not related.
- The subject is lost to follow-up.
- The subject is followed for 30 days after the End-of-Study Visit (or other appropriate time frame).
- The subject starts another investigational product.

9.3.5. Adverse Event Reporting

When an AE or SAE occurs, the investigator is responsible for reviewing all documentation (e.g., hospital progress notes, laboratory, and diagnostic reports) relative to the event(s). The investigator will record all relevant information about any AE (including SAEs) on the AE page of the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of the properly completed AE or SAE pages of the eCRF. These documents should not be sent unless they are specifically requested by the pharmacovigilance department. If this request occurs, all subject identifiers and protected health information should be blinded on the copies of the medical records before submission to the pharmacovigilance department and to the appropriate authorities.

The investigator will also attempt to report a diagnosis, instead of signs, symptoms, or other clinical information, for the AE. The diagnosis, not the individual signs and symptoms, should be documented on the appropriate page of the eCRF as the AE or SAE. In addition, SAEs need to

be reported in the SAE report. Aes being processed as SAEs will also require additional documentation. The study procedures manual provides additional guidelines about reporting SAEs.

9.3.6. Serious Adverse Event Reporting

1. Any SAE occurring after the subject signs the ICF and the study drug has been administered, as described in Section 9.3.2, must be reported to the Sponsor's or designee's pharmacovigilance department by phone, fax, or e-mail within 24 hours of the time the Investigator becomes aware of the SAE (Table 6). Any SAE reported by phone should be immediately followed up with the submission of the completed SAE report form. Urgent reporting of SAEs is required for the following reasons:
    a. To enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority
    b. To facilitate discussion between the Sponsor and the Investigator about appropriate follow-up measures (if necessary)
    c. To facilitate the Sponsor's rapid dissemination of information about AEs to other investigators or sites in a multicenter study
    d. To facilitate reporting unanticipated problems involving risk to subjects to the institutional review board (IRB) or independent ethics committee (IEC).

Table 6 Timeline for Reporting SAEs

Initial SAE Report		Follow-up SAE Report	
Time Frame	**Documents**	**Time Frame**	**Documents**
24 hours	SAE report	7 days	Updated SAE report

The SAE report will be completed as thoroughly as possible, including the following:

- Subject identification information
- Event term
- All available details about the SAE
- Causality of each SAE
- Signature of the Investigator

The SAE report will be forwarded to the Sponsor's or designee's pharmacovigilance department within the designated time frames. If additional information to complete the SAE report is needed, the Investigator will not wait before notifying the pharmacovigilance department of the SAE. The SAE report will be updated by the Investigator when additional information is received.

9.3.7. Reporting Events to Participants

Subjects will be given any new information that is learned about the study drug, or about their condition, during the course of the research study that might affect their willingness to continue participation. Subjects will be told about any new risks that become known during this research study.

9.3.8. Events of Special Interest

9.3.8.1. Gastrointestinal Event

Subjects taking HTD1801 may experience GI discomfort related to this therapy. This is variously described as diarrhea, abdominal bloating, abdominal discomfort, abdominal pain, and sometimes even constipation. Rather than have the subject discontinue and stop treatment altogether, downward dose titration from the starting dose of HTD1801 2000 mg per day is allowed and even encouraged.

Guidelines for dose reduction in the event of GI discomfort are outlined in Section 6.1.3.

9.3.8.2. Treatment Failure due to HTD1801 Dose Reduction

If any subject with PBC fails treatment after having their dose reduced, their study participation will be terminated and the subject would be able to resume their pre-study treatment for PBC after early termination study-required assessments completed. A subject will be considered to have failed treatment if the serum ALP, after having been lowered on treatment, returns to baseline or higher on two subsequent assessments (baseline is calculated as the average of the historical value and the value at screening).

9.3.8.3. Reporting of Pregnancy

When any member of the study staff becomes aware of a subject's (or subject's partner's) pregnancy, the site staff must report the pregnancy to the medical monitor and the within 24 hours by using the Pregnancy Notification Form. The female subject will discontinue study medication. The pregnancy will be followed until there is an outcome and the outcome is reported to the sponsor.

10. DRUG-INDUCED LIVER INJURY (DILI) MONITORING AND STOPPING RULES

It is important for study staff to monitor subjects for drug-induced liver injury and to educate subjects to recognize DILI symptoms and seek immediate medical attention.

Liver enzymes and serum bilirubin levels will be assessed at each clinic visit. Elevated ALTs will be assessed and dealt with as shown in Table 7 and Table 8.There are separate DILI monitoring plans based on whether the subject had normal or near normal versus elevated ALT values at baseline, because some subjects with PBC may have normal or near normal ALT levels at baseline. The Medpace Reference Laboratory (MRL) which will serve as the central laboratory for this study has defined its upper limit of normal for ALT as 53 U/L, in both males and females. The study therefore considers up to 60 U/L as being normal or near normal while >60 U/L is considered elevated.

Persistent Cholestatic liver injury is characterized by elevations in serum alkaline phosphatase and/or bilirubin (see Table 7 and Table 8).

10.1. Protocol Definition of Normal or Near Normal and Elevated ALT

10.1.1. Detection of Potential DILI in Subjects with Normal or Near Normal ALT levels at baseline

Because some subjects with PBC may have normal or near normal ALT levels at baseline (see Hirschfield 2015), an on-treatment ALT value more than 3x the ULN (i.e. >180 u/L) will be the threshold for triggering the DILI monitoring plan for these subjects.

10.1.2. Detection of Potential DILI in Subjects with Elevated ALT levels at baseline

Because subjects to be enrolled in the study have underlying liver disease, it is very likely that they may have an elevated ALT level at baseline and therefore multiples of the baseline will be used for DILI monitoring where the baseline value is elevated. The baseline ALT value will be calculated as the average of those obtained at the screening and baseline visits. An on-treatment ALT value more than 3x the baseline value will be the threshold for triggering the DILI monitoring plan for these subjects.

10.1.3. Process for DILI Monitoring

Serum ALT will be measured as part of a serum chemistry panel at screening, baseline and at weeks 2, 4, 6, 8 and 12. Serum samples will be shipped to a central or local laboratory for testing. Central lab reports will be faxed or emailed to the clinical site within 24 hours of receipt of the sample to be reviewed by the site PI. Local lab results will need to be entered into eDC. Values meeting or exceeding the DILI threshold described in Tables 7 and 8 will be flagged for the attention of the medical monitor. The medical monitor will contact the clinical site to initiate the DILI monitoring protocol.

Table 7: Liver Monitoring Procedure – For Subjects with Normal or Near Normal Baseline ALT (≤60 U/L)

Event	Observation	Action
ALT becomes elevated	Isolated increase in ALT to ≥3x ULN (i.e., ≥180 /L) with no increase in serum bilirubin and presence of symptoms of anorexia, nausea, fatigue, right upper abdominal discomfort or vomiting preceding or following the isolated increase in ALT to ≥3x ULN.	• Promptly repeat serum chemistry panel (ALT, AST, ALP, total bilirubin and direct bilirubin) within 2 to 5 days* • If subject lives remotely from the site, local labs may be obtained • The PI must review the local lab results promptly and local lab results must be entered into an unscheduled visit within the EDC • Continue investigational study drug
ALT remains elevated	If ALT remains ≥3x ULN	• Obtain serum chemistry panel (as above) and **repeat 2 – 3 x/week until stable** • Frequency of testing can be decreased to once per week or less if abnormalities stabilize or the subject is asymptomatic • Obtain detailed history of symptoms and prior or concurrent medical history • Obtain history of concomitant drug use including non-prescription medications, herbal & dietary preparations, alcohol use, recreational drug use, and special diets • Where appropriate, rule out acute viral hepatitis types A, B, C, D, & E, autoimmune or alcoholic hepatitis, NASH, hypoxic/ischemic hepatopathy & biliary tract disease • Obtain a history of exposure to environmental chemical agents • Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, CBC with differential) • Continue investigational study drug
ALT decreases	ALT return to <3x ULN or baseline level	• Resume study-required laboratory assessments as per the Summary of Events table and continue investigational study drug
Elevated Liver Function Tests Worsen or Clinical Symptoms Develop	If ALT is >8x ULN of baseline on one occasion, or If ALT is >5x ULN of baseline for more than 2 weeks, or If ALT is >3x ULN of baseline AND bilirubin is >2X ULN OR INR >1.5), or	• **Permanently STOP** investigational study drug • Continue monitoring until all abnormalities return to normal or to the baseline state • All DILI monitoring results must be recorded in the DILI monitoring eCRF

	If ALT is >3x ULN of baseline AND subject is symptomatic (severe fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Persistent Cholestatic Liver Injury	If serum ALP is >2x ULN and total and direct bilirubin is >2x ULN	• **Permanently STOP** investigational study drug • Continue monitoring until all abnormalities return to normal or to the baseline state • All DILI monitoring results must be recorded in the DILI monitoring eCRF

* The PI must review the local lab results promptly. Local lab results must be entered into an unscheduled visit within the EDC

Table 8: Liver Monitoring Procedure – For Subjects with Calculated Baseline ALT >60 U/L (Elevated ALT)

Event	Observation	Action

ALT becomes elevated	Isolated increase in ALT to ≥3x ULN (i.e., ≥180 u/L) with no increase in serum bilirubin and presence of symptoms of anorexia, nausea, fatigue, right upper abdominal discomfort or vomiting preceding or following the isolated increase in ALT to >3x ULN.	• Promptly repeat serum chemistry panel (ALT, AST, ALP, total bilirubin and direct bilirubin) within 2 to 5 days*
		  • If subject lives remotely from the site, local labs may be obtained
		  • The PI must review the local lab results promptly and local lab results must be entered into an unscheduled visit within the EDC
		  • Continue investigational study drug

ALT remains elevated	If ALT remains ≥3x calculated baseline	• Obtain serum chemistry panel (as above) and **repeat 2 – 3 x/week until stable** • Frequency of testing can be decreased to once per week or less if abnormalities stabilize or the subject is asymptomatic • Obtain detailed history of symptoms and prior or concurrent medical history • Obtain history of concomitant drug use including non-prescription medications, herbal & dietary preparations, alcohol use, recreational drug use, and special diets. • Where appropriate, rule out acute viral hepatitis types A, B, C, D, & E, autoimmune or alcoholic hepatitis, NASH, hypoxic/ischemic hepatopathy & biliary tract disease • Obtain a history of exposure to environmental chemical agents • Obtain additional tests to evaluate liver function, as appropriate (e.g., INR, CBC with differential) • Continue investigational study drug
ALT decreases	ALT return to <3x ULN or baseline level	• Resume study-required laboratory assessments as per the Summary of Events table and continue investigational study drug
Elevated Liver Function Tests Worsen	If ALT is >8x ULN of calculated baseline on one occasion, or If ALT is >5x ULN of calculated baseline for more than 2 weeks, or If ALT is >3x ULN of calculated baseline AND bilirubin is >2X ULN OR INR >1.5), or	• **Permanently STOP** investigational study drug • Continue monitoring until all abnormalities return to normal or to the calculated baseline state • All DILI monitoring results must be recorded in the DILI monitoring eCRF

	If ALT is >3x ULN of calculated baseline AND subject is symptomatic (severe fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Persistent Cholestatic Liver Injury	If serum ALP is >2x ULN and total and direct bilirubin is >2x ULN	• **Permanently STOP** investigational study drug • Continue monitoring until all abnormalities return to normal or to the calculated baseline state • All DILI monitoring results must be recorded in the DILI monitoring eCRF

* The PI must review the local lab results promptly. Local lab results must be entered into an unscheduled visit within the EDC

11. COVID-19 PANDEMIC CONTINGENCIES

11.1. Potential Impact of COVID-19 on Study Conduct

The potential impact from quarantine restrictions, site closures and travel restrictions may limit the site's and subject's capability to have on-site visits.

11.2. Operational Contingencies related to COVID-19 Pandemic

Local site policies and process for COVID-19 monitoring, for example, temperature check, COVID-19 exposure history, recent travel history and use of personal protective equipment must be followed.

The study protocol specifies that all visits are in-clinic visits but allows for contingency measures for Study Visits Week 2, 4, 8, 16 and the Early Termination visit in the occurrence where a subject is unwilling or unable to participate in an in-clinic visit due to the COVID-19 pandemic.

In that instance, the site will work with the study subject to obtain study-required blood draws at a local laboratory or arrangements will be made to have the home health provider obtain the visit specific blood draw for the study-required laboratory assessments.

Other visit assessments will have to occur via a remote visit by telephone or a video conference, per site practice and procedures, to assess changes in the subjects' health condition, make note of any changes in concomitant medications, and inquire about adverse events. The visit must be documented as a telephone/video conference visit with arrangements for laboratory assessments.

The site will enter the laboratory results, if obtained at a local laboratory, into the EDC as an "unscheduled" visit that will be mapped to the specific visit for which local laboratory data were obtained. If the visit specific blood draw is obtained by the home health service provider, it will be shipped to the central laboratory; the results will be entered into the central laboratory database and merged with the clinical database at the completion of the study.

Every effort must be made to complete the full scope of the study visit activities and procedures. Any deviation from the procedures and protocol-specified contingency measures due to COVID-19 must be clearly documented as COVID-19-related and reported to the IRB as applicable.

The PI and study personnel are responsible for ensuring full investigational product accountability.

12. STATISTICAL CONSIDERATIONS

12.1. Statistical Hypotheses

The primary hypothesis for this study is that treatment with HTD1801 results in reductions in ALP:

$$H_0: \frac{ALP_{Week\ 12} - ALP_{Baseline}}{ALP_{Baseline}} \geq 0 \; vs. \; H_a: \frac{ALP_{Week\ 12} - ALP_{Baseline}}{ALP_{Baseline}} < 0$$

The estimand will be the percent change from baseline and will be measured within all subjects on treatment and who provide data at Week 12. This estimand is similar to the While on Treatment Strategy outlined in ICH e9 R1 but is limited to on treatment results at Week 12 (i.e., results from prior to Week 12 are not included in the analysis of the Week 12 results).

Testing will be one sided using a 5% alpha level.

12.2. Sample Size Determination

A sample size of 30 subjects provides ≥90% power for the primary endpoint assuming a mean percent reduction in ALP of 15% and a SD of 25%. Power calculations use a 5% one sided alpha and a t-test. Sample size calculation were performed in PASS (PASS 2014).

12.3. Populations for Analyses

The following analysis populations will be defined for statistical analysis:

- Screened population
  - The Screened population will consist of all subjects who sign the study informed consent.
- Intention-to-treat (ITT) population
  - The ITT population will consist of all subjects that receive at least one dose of HTD1801. This population will be used for all efficacy, safety, and baseline/demographic analyses and summaries.
- Population undergoing pharmacokinetic testing
  - At least 6 subjects will undergo sparse PK sampling at weeks 6 and 12.

12.4. Statistical Analyses

12.4.1. General Approach

Endpoints will be summarized using descriptive statistics. For continuous variables n (number of subjects with data), mean, standard deviation, median, minimum, and maximum will be used. For categorical results the number of subjects and the percent of subjects per category will be summarized. Confidence intervals will be generally reported using 95% two-sided confidence intervals. When testing is used p-values with four decimal places will be reported; no adjustment for multiplicity will be conducted.

Missing data will not be imputed for the efficacy analyses. Missing dates for adverse events and concomitant medication will be imputed to allow these items to be summarized as on or off treatment.

12.4.2. Analysis of the Primary Efficacy Endpoint(s)

Alkaline phosphatase levels, change from baseline, and percent change from baseline will be summarized with descriptive statistics and 95% normal approximation confidence intervals. Testing for the percent change endpoint using a t-test will also be performed. Given the limited sample size (i.e. less than 30 subjects) and the potential for right skewed data the normality assumption may not be fully accurate. Hence, the true alpha level may theoretically not be 5%. As such, these tests will be considered descriptive more than confirmatory.

12.4.3. Analysis of the Secondary Endpoint(s)

The secondary endpoints including the secondary ALP endpoints will be summarized using descriptive statistics. Summary statistics at each timepoint that data is captured will be provided for the result as well as the change from baseline, when change from baseline is applicable. Confidence intervals will be produced for changes in serum bilirubin and change in gamma-glutamyl transferase.

12.4.4. Safety Analyses

Safety endpoints will be summarized using descriptive statistics.

Treatment emergent adverse events (TEAE), events that start on or after the start of treatment, will be summarized by system organ class and preferred term. Summaries of all TEAEs, treatment emergent SAEs, related TEAEs and TEAEs by severity will be produced.

Laboratory, vital sign, and ECG results will be summarized as continuous measures (e.g., change from baseline). Selected laboratory results will also be summarized as categorical variables (e.g., ‘in’ versus ‘out’ of the normal range).

12.4.5. Pharamacokinetic Analyses

Descriptive statistics will be summarized for plasma concentrations of BBR and UDCA as a function of study visit. These concentrations will be used to build a population PK model in combination with PK data from other studies to inform model-derived parameters, if applicable.

12.4.6. Baseline Descriptive Statistics

Subjects who discontinue treatment or withdraw from the study, and the reasons for doing so, will be summarized. Subject demographic and baseline characteristics will be summarized.

12.4.7. Planned Interim Analyses

Enrollment into the study may be stopped early prior to enrollment of 30 subjects should the scientific goal (evaluate the effects of HTD1801 on serum ALP) of the study be achieved with the currently available data. That is, if prior to enrollment of 30 subjects if the results are robust enough to provide preliminary evidence of efficacy that warrant further evaluation in a placebo-controlled study, enrollment in this study may be terminated.

13. STUDY ADMINISTRATION

13.1. Informed Consent and Authorization For Use and Disclosure of Protected Health Information

Written informed consent and authorization of use and disclosure of protected health information must be obtained from each subject (or the subject's legally acceptable representative) before performing any study-specific Screening or Baseline evaluations. One copy of the signed ICF and authorization for use and disclosure of protected health information form will be given to the subject, and the Investigator will retain the original. The ICF and authorization for use and disclosure of protected health information, which is prepared by the Investigator or the investigational site, must have been reviewed and approved by the Sponsor, the Study Monitor, and the Investigator's IRB or IEC and privacy board (if separate from the IRB/IEC) before the initiation of the study. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The authorization for use and disclosure of protected health information must contain the elements required by Title 45 of the Code of Federal Regulations, Section 164.508(b), and any local regulations for valid authorizations.

13.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigators and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

13.3. Study Documentation

13.3.1. Investigator Information

Investigator information is included in the SPM (or other applicable instructions), which is updated as needed.

13.3.2. Investigator's Study Files

Documentation about the Investigator and his/her study staff, the IRB/IEC, and the institution is required before site initiation. Copies of these documents will be kept on site in site specific binders or electronic folders, along with the following supplemental information: a list of Investigator's obligations; the Investigator's Brochure; the clinical protocol and amendments; safety information; information about the investigational product, biological samples, and the applicable laboratory(ies); the SPM (or other applicable instructions) and study logs; eCRFs; records of monitoring activities; and correspondence between the Sponsor or Study Monitor and the Investigator.

13.3.3. Case Report Forms and Source Documentation

The Investigator must make study data accessible to the Study Monitor, other authorized representatives of the Sponsor, and the appropriate regulatory authority inspectors. The eCRF for each subject will be checked against source documents at the investigational site by the Study Monitor, and a final copy of the eCRF will be signed by the Investigator with an electronic signature. A copy of the final eCRFs will be provided to the Investigator in PDF format on computer disc after study closure to be kept in the Investigator's study files.

13.3.4. Retention of Study Documents

According to ICH E6, Section 4.9, all eCRFs, as well as supporting paper and electronic source documentation and administrative records, must be retained by the Investigator until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor is responsible for informing the Investigator and institution as to when these documents no longer need to be retained. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another Investigator at the institution where the study was conducted.

Audit trails for electronic documentation must be retained for a period at least as long as the period required for the subject's electronic records to which they pertain. The Investigator must retain either the originals of the audit trails or a certified copy of the audit trails.

13.4. Confidentiality

13.4.1. Data

The Investigator must keep all information confidential about the nature of the proposed investigation provided by the Sponsor or Study Monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/IEC, the subject, or the appropriate regulatory authority).

13.4.2. Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject ID number on eCRFs and other documents retrieved from the investigational site or sent to the Study Monitor, Sponsor, regulatory agencies, central laboratories, or blinded reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

13.5. Protocol Compliance

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject-selection criteria. Such changes must be prepared as a protocol amendment by the Sponsor and implemented only upon joint approval of the Sponsor and the Investigator. A protocol amendment must receive IRB/IEC approval before implementation. In parallel with the IRB/IEC approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the ICF, the revised ICF prepared by the Investigator must also be approved by the Sponsor, Study Monitor, and the IRB/IEC before implementation.

Departures from the protocol eligibility criteria (see Sections 5.1 and 5.2) are not permitted as these could jeopardize subject safety, study integrity, or regulatory acceptance of the results.

Departures from other protocol procedures or requirements are allowed only in situations that eliminate an immediate risk to a subject and that are deemed crucial for the safety and wellbeing of that subject. The Investigator or the attending physician will also contact the Medical Monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB/IEC; however, the IRB/IEC and Medical Monitor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the subject's eCRF the reasons for the protocol deviation and the ensuing events.

13.6. Study Monitor Functions and Responsibility

The Study Monitor, in accordance with the Sponsor's requirements, will ensure that the study is conducted and documented properly by carrying out the activities outlined in ICH E6, Section 5.18.4.

13.7. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.8. General Information

The Investigator should refer to the Investigator's Brochure, SPM (or other applicable instructions), and any other information provided about the investigational product and details of the procedures to be followed during this study.

14. ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AIH	autoimmune hepatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANA	antinuclear antibody
AST	aspartate aminotransferase
BBR	berberine
BID	twice daily
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CRP	C-reactive protein
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELF	enhanced liver fibrosis
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
G6PD	glucose-6-phosphate dehydrogenase
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HDL-c	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
ITT	intention-to-treat
LDL-c	low-density lipoprotein cholesterol
NASH	nonalcoholic steatohepatitis
OCA	obeticholic acid
PBC	primary biliary cholangitis
PSC	primary sclerosing cholangitis
SAE	serious adverse event
SD	standard deviation
SPM	Study Procedures Manual
TEAE	treatment-emergent adverse event

TSH	thyroid stimulating hormone
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VAS	visual analogue scale

15. REFERENCES

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APPENDIX A. GLOBE SCORE

https://www.globalpbc.com/globe

The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk.

Age, years *at initiation of UDCA therapy*			
Total bilirubin level, µmol/L or mg/dl *after one year of UDCA therapy*		Upper limit of normal:	
Alkaline phosphatase level, U/L *after one year of UDCA therapy*		Upper limit of normal:	
Albumin, g/L *after one year of UDCA therapy*		Lower limit of normal:	
Platelets, x 10^9/L *after one year of UDCA therapy*			

Interpretation of the GLOBE score:

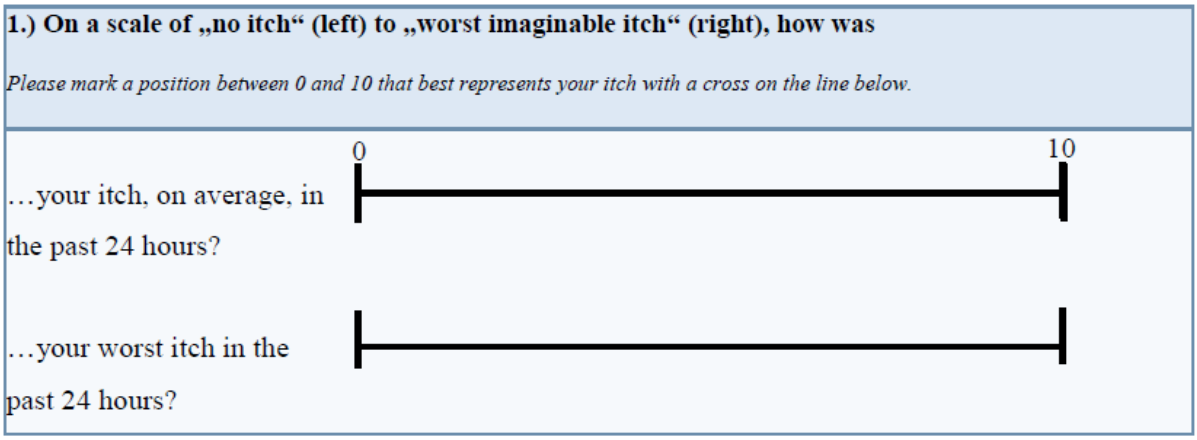
Patients with a GLOBE score corresponding with an estimated transplant-free survival comparable with an age- and sex-matched population are at low risk for future adverse events and patients with a GLOBE score corresponding with a transplant-free survival that significantly deviates from an age- and sex-matched population may benefit from new therapies

Data of an age- and sex-matched population, a population with a life-expectancy comparable with that of other countries participating in the Global PBC Study Group, were retrieved from a Dutch registry (Statistics Netherlands, www.cbs.nl).

The GLOBE score uses age-specific thresholds beyond which survival significantly deviates from an age- and sex matched general population. In subgroups of patients aged 66 years, age-specific GLOBE-score thresholds beyond which survival significantly deviates from matched individuals are 0.52, 0.01, 0.60, 1.01 and 1.69, respectively.

APPENDIX B. PRURITUS VAS SCORE

Visual Analogue Scale (VAS)



http://www.pruritussymposium.de/visualanaloguescale.html

Scoring:

VAS 0= No pruritus

VAS < 3= Mild pruritus

VAS ≥ 3-<7= Moderate pruritus

VAS ≥ 7-<9 = Severe pruritus

VAS ≥ 9= Very severe pruritus