CONFIDENTIAL

CLINICAL PROTOCOL

TITLE OF STUDY:

A Proof-of-Concept and Dose-Ranging Study Investigating the Efficacy and Safety of HTD1801 in Adult Subjects with Primary Sclerosing Cholangitis (PSC)

Protocol HTD1801.PCT003

Trial Registration: **NCT03333928**

Date of issue: **07 January 2019**

Version number: **1.4PK**

Sponsor: **HighTide Biopharma Pty. Ltd.**
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Signatures of Approval of Protocol (Version 1.4PK)

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STUDY SYNOPSIS

Name of sponsor company: HighTide BioPharma Pty. Ltd.	
Name of finished product: HTD1801 Tablets	
Name(s) of active ingredient(s): Berberine Ursodeoxycholate (HTD1801)	
Title of study: A Proof-of-Concept Study Investigating the Efficacy and Safety of HTD1801 in Adult Subjects with Primary Sclerosing Cholangitis (PSC)	
Investigator(s): TBD	
Number of sites: TBD	
Study period: 18 weeks	**Phase of development:** 2

Objectives:

The primary objective of this proof-of-concept study is to evaluate the effects of HTD1801 on alkaline phosphatase (ALP) in adult subjects with PSC.

The secondary objectives of this study are to evaluate the effects of HTD1801 on concurrent disease activity of inflammatory bowel disease (IBD), and on the safety and tolerability of HTD1801 over 18 weeks in adult subjects with PSC.

Pharmacokinetic (PK) and pharmacodynamics (PD) objectives include:

- Develop and validate population PK models for the components of HTD1801: berberine (BBR) and ursodeoxycholic acid (UDCA);
- Calculate individual single-dose and steady-state exposure metrics based on non-compartmental analysis methods in adult patients with PSC;
- Evaluate exposure-response models for efficacy;
- Evaluate the relationship between exposure, adverse events, and serious adverse events.

Methodology: A 6-week randomized, double-blind, placebo- and dose-controlled, parallel group clinical trial with a PK substudy, followed by a 6-week, dose-controlled extension period, followed by a 6-week placebo controlled randomized withdrawal period.

Number of subjects (planned): 90 subjects in total. If a subject discontinues from the study for any reason other than safety prior to the first post-dose assessment, a replacement subject may be enrolled. Approximately 36 subjects enrolled at selected sites will undergo additional blood draws for PK/PD analysis.

Inclusion criteria:

1. Male or female between 18 and 75 years of age;
2. Have a clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis;
3. If subjects have Inflammatory Bowel Disease (IBD) they will be eligible to participate. If a subject has IBD, documented evidence of IBD must have been evident by prior endoscopy or in previous medical records for ≥6 months. In addition, subjects may only enter the study with a

STUDY SYNOPSIS (continued)

Name of sponsor company: HighTide BioPharma Pty. Ltd.

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Partial Mayo Score of 0-4, inclusively. Subjects who are on treatment are allowed, provided they are stable for 3 months if taking:

a. 5-amino salicylic acid drugs,

b. azathioprine,

c. 6-mercaptopurine, or methotrexate

d. biologics;

4. Have a serum ALP ≥1.5 × upper limit of normal (ULN);
5. Females of child-bearing potential and males participating in the study must either agree to use at least 2 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 3 months after stopping study drug. Females who are postmenopausal must have appropriate documentation;
6. Be able to understand and sign a written informed consent form (ICF);
7. Subjects receiving allowed concomitant medications need to be on stable therapy for 28 days prior to the Baseline visit, with the exception of ursodeoxycholic acid (UDCA), which should be stable for at least 6 weeks prior to the Baseline visit.

Exclusion criteria:

1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations;
2. Small duct PSC;
3. Presence of percutaneous drain or bile duct stent;
4. History of cholangiocarcinoma or clinical suspicion of new dominant stricture within 1 year by MRCP/ERCP. Presence of dominant stricture without ERCP evidence of cholangiocarcinoma is acceptable if stable for ≥ 1 year.;
5. Ascending cholangitis within 60 days prior to Screening;
6. Concomitant overlap syndrome with autoimmune hepatitis (AIH) as diagnosed by AST or ALT > 5x ULN, AND
   i. positive smooth muscle antibody and/or liver-kidney microsomal antibody (LKM), or
   ii. IgG >ULN, or
   iii. Biopsy suggestive for AIH
7. Concomitant overlap syndrome with primary biliary cholangitis (PBC) as diagnosed by either:

STUDY SYNOPSIS (continued)

Name of sponsor company: HighTide BioPharma Pty. Ltd.

Name of finished product: HTD1801 Tablets

Name(s) of active ingredient(s): Berberine Ursodeoxycholate (HTD1801)

i. positive AMA, or

ii. biopsy suggestive for PBC

8. **History of alcohol or substance abuse or dependence**;
9. Prior or planned liver transplantation;
10. Presence of alternative causes of chronic liver disease, including alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis;
11. Platelet count below 125,000/mm^3, albumin below 3.0 g/dL, International Normalized Ratio (INR) > 1.2, or a history of ascites, or encephalopathy, or history of esophageal variceal bleeding;
12. Anticoagulant therapy, with the exception of acetylsalicylic acid;
13. Severe active IBD or flare in colitis activity within the last 90 days requiring intensification of therapy beyond baseline treatment;
14. Use of oral prednisone/prednisolone > 10 mg/day;
15. Hospitalization for colitis within 90 days;
16. AST > 5 x ULN;
17. ALT > 5 x ULN;
18. Total bilirubin > **1.2 x** ULN. **If total bilirubin result at screening is > ULN but ≤ 1.2 x ULN, a confirmatory total bilirubin should be collected after 21 days. If the confirmatory total bilirubin remains ≤ 1.2 x ULN, and all other eligibility criteria continue to be met, the subject will be eligible.**;
19. Evidence of Gilbert's Syndrome;
20. Immunoglobulin G4 (IgG4) > 2 × ULN at screening or evidence of IgG4-related sclerosing cholangitis;
21. **Estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m^2, calculated by the local laboratory**;
22. Hemoglobin < 10 g/dL for males or females;
23. Hepatitis B surface antigen positive;
24. Hepatitis C antibody positive;
25. Human immunodeficiency virus (HIV)-1 or HIV-2 infection;
26. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
27. History of malignancy within the past 2 years or ongoing malignancy other than basal cell carcinoma, or resected noninvasive cutaneous squamous cell carcinoma;
28. Active, serious infections that require parenteral antibiotic or antifungal therapy within 30 days prior to Screening;
29. Major surgical procedure within 30 days of Screening or prior organ transplantation;
30. Females who are pregnant or breastfeeding;

STUDY SYNOPSIS (continued)

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31. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents and immune-modulating agents (such as systemic corticosteroids, interleukins, interferons);
32. Allergy to the clinical trial material or its components;
33. Received any experimental medications within 30 days prior to Screening;
34. 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: 500 mg or 1000 mg administered as tablets twice daily with food
Placebo: Administered as tablets twice daily with food

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

Duration of treatment: Up to 18 weeks

Criteria for Evaluation:

Efficacy Evaluation

Efficacy endpoints:

The primary endpoint for this study is the change in serum alkaline phosphatase (ALP) between Baseline and Week 6.

Secondary endpoints will include:

1. Change in serum ALP between Baseline and Weeks 12 or 18, dependent upon the length of continuous treatment, compared to the placebo response during Period 1;
2. Change in serum ALP between a new baseline at Week 6 and the final value at Weeks 12 for those subjects who received placebo during Period 1, compared to their initial 6-week placebo response;
3. Change in serum ALP between a new baseline at Week 6 and the final value at Weeks 12 for those subjects who received placebo during Period 1, compared to the similar change in the 500 mg and 1,000 mg treatment groups;
4. Change in serum ALP between a new baseline at Week 12 and the final value at Weeks 18 for all subjects following the randomized withdrawal;
5. Proportion of patients who achieve ALP of <1.5 x ULN;
6. Proportion of patients who achieve a 50% decrease in ALP;
7. The proportion of patients who normalize ALP;
8. Change in AST/ALT ratio;

STUDY SYNOPSIS (continued)

Name of sponsor company: HighTide BioPharma Pty. Ltd.

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9. Change in serum bilirubin;
10. In subjects with IBD who have elevated FC, change in FC compared to Baseline at Weeks 6 and 12, and the proportion of subjects who normalize FC at Weeks 6 and 12;
11. For subjects who have elevated CRP at Baseline (for all subjects as well as only IBD subset): change from Baseline in CRP at Weeks 6 and 12, and normalization of CRP at Weeks 6 and 12;
12. For subjects with IBD who have Partial Mayo Score above 0: Change from Baseline in Mayo scores at Weeks 6 and 12.

Efficacy analysis:

The mITT population will be used for the analysis of all efficacy endpoints. The primary efficacy variable is the change in ALP from Baseline to Week 6 in the initial double-blind parallel group period. Changes in ALP from Baseline will be summarized by treatment group, visit and treatment period using descriptive statistics. A mixed model repeated measures (MMRM) will be fit to the data and the model will include fixed factors for treatment, visit and treatment by visit interaction, a random factor for subject, and Baseline value as a covariate. An unstructured covariance matrix will be used to model the repeated assessment over time. Denominator degrees of freedom will be adjusted using Kenward-Roger's method. Sensitivity analyses will be described in the statistical analysis plan (SAP). Treatment comparisons will be made at each visit and each treatment period, with the primary comparison at Week 6. No imputation of missing data is necessary for the MMRM analysis of the primary endpoint. A similar MMRM analysis will be performed for the randomized withdrawal period. Analysis for the randomized withdrawal period will be conducted for all subjects and separately for responders based on pre-specified responder criteria. For the dose-controlled treatment period, a one sample t-test will be used to evaluate the change in ALP from Week 6 to Week 12 for the subjects who were previously randomized to placebo during the first period.

The secondary efficacy variables of the proportion of subjects whose ALP values normalize, the proportion of subjects whose ALP values decrease below 1.5 x ULN, and the proportion of subjects who achieve a 50% decrease in ALP from Baseline will be calculated at end of treatment using a last observation carried forward for any missing data. Frequencies and percentages will be calculated by treatment group and by visit. Any adjustments for multiplicity will be described in the SAP. Treatment comparisons will be made at Week 6 (or LOCF) using Fisher's exact test. A similar analysis will be performed for the randomized withdrawal period. For the dose-controlled extension period, a one sample exact test will be used to evaluate the proportion of subjects achieving each of the secondary endpoints at Week 12 for the subjects who were randomized to placebo during the double-blind period. The secondary efficacy variables of change from Baseline in AST/ALT ratio, bilirubin, C-reactive protein and fecal calprotectin will be analyzed using a MMRM similar to that described above for the primary efficacy variable.

STUDY SYNOPSIS (continued)

Safety Evaluation

Safety Endpoints:
Adverse events and changes in clinical laboratory assessments will be used to evaluate safety and tolerability.

Safety Analysis:
Safety data will be summarized using descriptive analysis.

PK/PD Evaluation

Pharmacokinetic Endpoints:
1. Apparent clearance (CL/F) of UDCA and BBR;
2. Apparent volume of distribution at steady state (V_{ss}/F) for UDCA and BBR;
3. Additional single-dose and steady-state non-compartmental exposure metrics (e.g., C_{max}, $AUC_{0\text{-}12}$, $AUC_{0\text{-}inf}$).

Population Pharmacokinetic Analysis:

Population PK models for the components of HTD1801 will be developed and validated using a nonlinear mixed-effects model (NONMEM) approach. Selection of the appropriate model will be based on hypothesis testing and graphical analysis of residual error (goodness of fit). Target parameters for each component include apparent clearance (CL/F) and apparent volume of distribution at steady state (V_{ss}/F). Covariate relationships will be evaluated and incorporated into the model as indicated by the data. Covariates for evaluation will include, but will not be limited to, vital signs (e.g., body size), demographics (e.g., sex, age, race) and organ function / disease biomarkers (e.g., bilirubin and alkaline phosphatase). The models will be validated using likelihood profiles, bootstrap analysis, and visual predictive check.

Concentration vs. time profiles will be simulated for each subject based on that subject's individual-specific (post-hoc) parameter estimates. Individual single-dose and steady-state non-compartmental metrics will be calculated from these simulated data. Metrics for UDCA will be reported with and without baseline correction.

Pharmacokinetic/Pharmacodynamic Analysis

An exploratory exposure-response analysis will be performed to evaluate the relationship between exposure metrics (e.g., AUC, C_{max}) for UDCA, BBR, and UDCA+BBR and change from baseline in serum ALP. The analysis will evaluate the effect of covariates including disease state (e.g., baseline ALP; IBD with elevated FC; elevated CRP).

An exploratory exposure-response analysis will be performed to evaluate the relationship between exposure, adverse events (AE) of interest, and serious adverse events (SAE). The relationship between exposure and AE or SAE occurrence will be evaluated graphically and, where indicated, statistically.

STUDY SYNOPSIS (continued)

Name of sponsor company: HighTide BioPharma Pty. Ltd.
Name of finished product: HTD1801 Tablets
Name(s) of active ingredient(s): Berberine Ursodeoxycholate (HTD1801)
Study Design: The entire study is randomized and double blind, with a concurrent placebo control except in Period 2. Randomization will be stratified based on presence of IBD. Period 1: Placebo and dose controlled (6 weeks) Each subject will be randomized to one of three groups: a) placebo twice daily with food; b) 500 mg of HTD1801 twice daily with food; or c) 1000 mg of HTD1801 twice daily with food. Period 2: Dose-controlled extension (6 weeks) Subjects previously randomized to 500 mg BID will continue receiving 500 mg. Subjects previously randomized to 1000 mg BID will continue receiving 1000 mg. Subjects previously randomized to PBO BID will be randomized to receive either 500 mg or 1000 mg. Period 3: Randomized withdrawal (6 weeks) All subjects will be randomized to either remain on the treatment assigned in Period 2 or to placebo (PBO).

Figure 1. Study Design

Screening	Baseline/ Randomization/ Dosing	Initial Dosing Period			Dose-controlled Extension			Randomized Withdrawal			Follow-up
Days -28 to -1	Day 0/1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 22

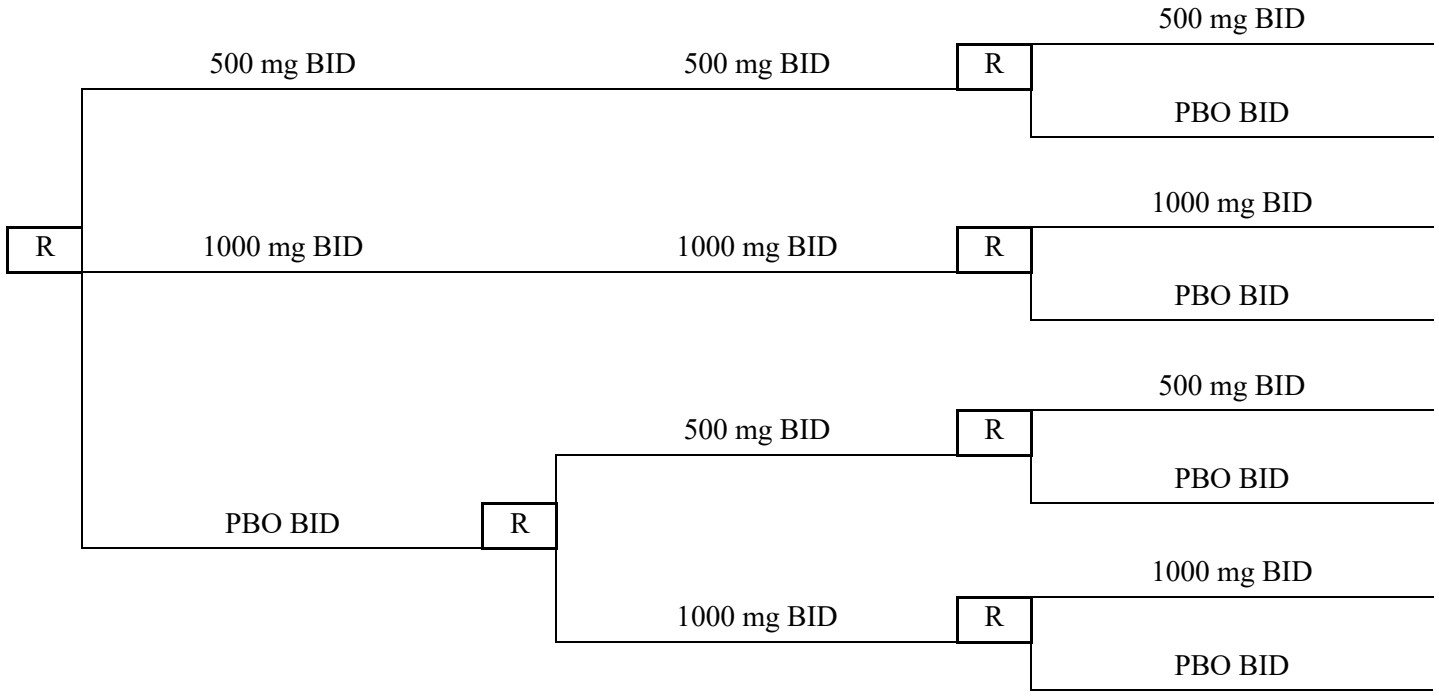

Figure 1PK. Pharmacokinetic Substudy Design

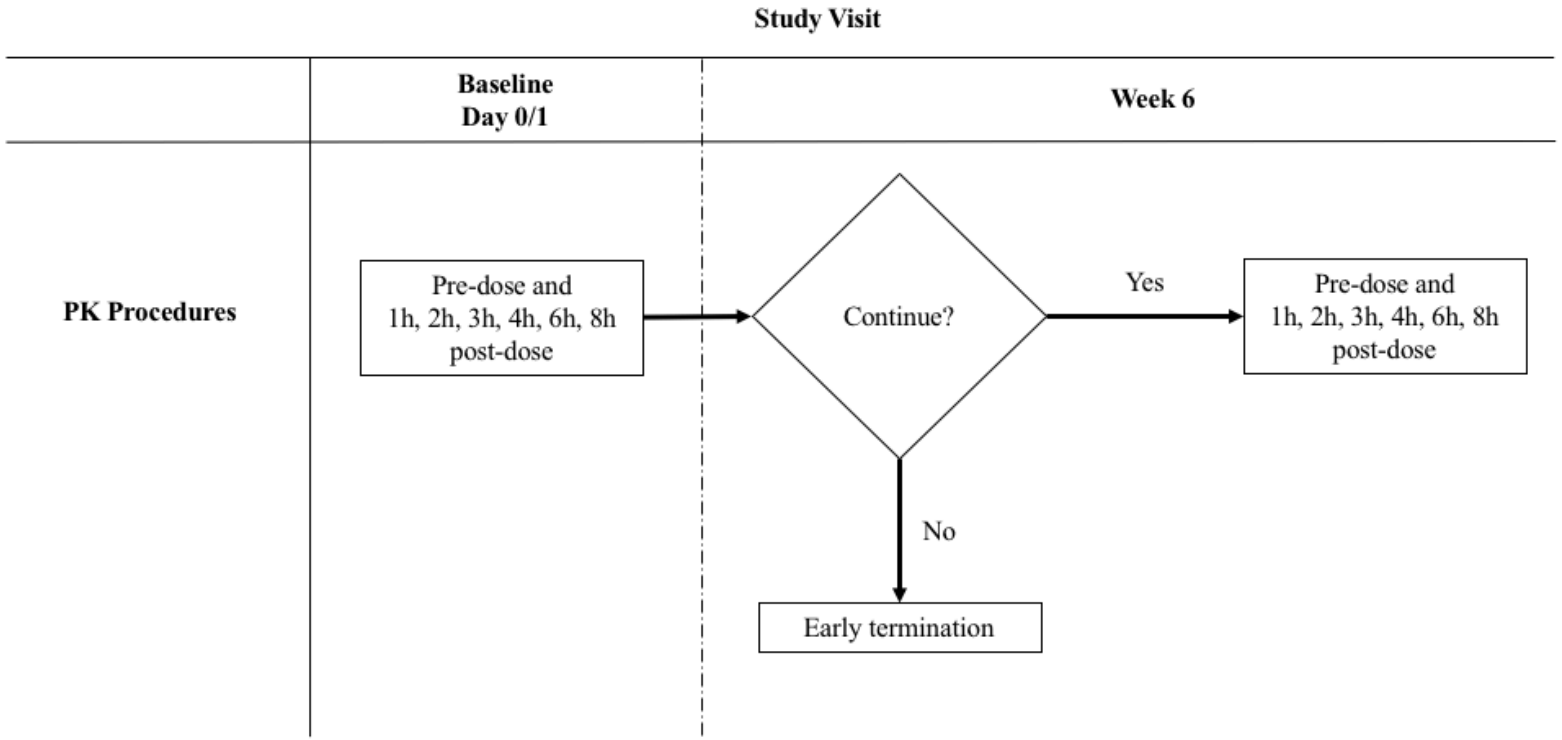

Table 1. Schedule of Time and Events

	Screening	Baseline/ Rand/ Dosing	Initial Dosing Period			Dose-controlled Extension			Randomized Withdrawal			Follow-up
	Days -28 to -1	Day 0/1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 22
Procedure												
Clinic Visits	X	X			X			X			X	
Informed consent	X											
Eligibility criteria	X	X										
Demographics	X											
G6PD	X											
IgG4	X											
Urine drug test	X											
HIV/Hepatitis B, C	X											
Medical history	X	X										
Concomitant meds	X	X			X			X			X	X
Physical examination	X	X			X			X			X	
Ht., Wt., Vitals	X	X			X			X			X	
ECG	X	X			X			X			X	
Pregnancy testing	X	X									X	
Partial Mayo Score	X	X			X			X			X	
CBC, CMP **, Lipids	X	X	X	X	X	X	X	X	X	X	X	
INR	X	X			X			X			X	
Mayo Risk Score		X										
C-reactive protein *		X			X			X			X	
Fecal calprotectin *		X			X			X			X	
Randomization		X			X			X				
Dosing		X	X	X	X	X	X	X	X	X	X	
PK sampling***		X			X							
Dosing diary ***					X							
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X
Telephone contact			X	X		X	X		X	X		X
Discharge											X	

* IBD subset only
** Including GGT
*** PK substudy only

Table 1PK. Pharmacokinetic Sampling Schedule

Timepoint	Baseline	Week 6
Pre-dose	X	X
+1 hour post-dose	X	X
+2 hours post-dose	X	X
+3 hours post-dose	X	X
+4 hours post-dose	X	X
+6 hours post-dose	X	X
+8 hours post-dose	X	X

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AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BBR	berberine
BBR·Cl	berberine chloride
BDL	bile duct ligation
BID	twice daily
CBC	complete blood count
CMP	comprehensive metabolic panel
CRF	case report form
DILI	drug induced liver injury
eCRF	electronic case report form
eGFR	**estimated glomerular filtration rate**
ERCP	endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG4	Immunoglobulin G4
IP	investigational product
IRB	institutional review board
MCRP	magnetic resonance cholangiopancreatography
mITT	modified intent-to-treat
PBC	primary biliary cirrhosis
PBO	placebo
PSC	Primary Sclerosing Cholangitis
SAE	serious adverse event
SPM	study procedures manual
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

1.0 INTRODUCTION

HTD1801 is a novel salt formed between berberine (BBR) and ursodeoxycholic acid (UDCA) with a stoichiometry of 1:1, and is currently being developed as an oral treatment of primary sclerosing cholangitis (PSC). HTD1801 is expected to dissociate into berberine chloride (BBR·Cl) and UDCA after oral administration. Both UDCA and BBR have demonstrated efficacy in the treatment of cholestatic disease. 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 PSC by assessing effects of alkaline phosphatase (ALP) over 6 weeks.

1.1 BACKGROUND

1.1.1 Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic, progressive liver disease characterized by inflammation and fibrosis of the intra- and/or extra-hepatic bile ducts, which leads to the formation of multifocal bile duct strictures. This cholestatic disease leads to fibrosis and ultimately liver failure, cirrhosis and an increased risk of malignancy.[1, 2] Today, nearly 50,000 patients in the United States suffer from PSC, and the median life expectancy after diagnosis of PSC is 12 to 18 years without liver transplantation.[3] PSC is more common in men than in women (2:1), and can occur at any age with a peak incidence around forty years of age.[4]

Currently, no effective therapy has been approved for the treatment of PSC.[1] UDCA is a secondary bile acid produced by intestinal bacteria as a metabolic by-product, which is approved by the Food and Drug Administration (FDA) in the United States for the treatment of primary biliary cirrhosis (PBC) (NDA 020675).[5] UDCA has been shown to significantly improve biochemical parameters, delay progression of the disease and prevent the need for liver transplantation in patients with PBC.[6, 7] The possible mechanisms of action for UDCA's efficacy in the treatment of chronic cholestasis include, but are not limited to, the following:[8]

- Improvement of hydrophilicity index in the circulating bile acid pool;
- Stimulation of hepatobiliary and ductular secretion;

- Cytoprotection against bile acid and cytokine-induced injury;
- Immunomodulation and anti-inflammatory effects.

Based on the pharmacological properties summarized above, UDCA has been investigated as a potential therapeutic agent for the treatment of patients with PSC. UDCA treatment leads to significant improvements in liver biochemistry, including serum ALP, aspartate transaminase (AST), and bilirubin. However, a meta-analysis failed to show that UDCA reduced mortality, hepatic decompensation, need for liver transplantation or liver histological deterioration compared with placebo.[9, 10] Tabibian et al., pointed out that UDCA monotherapy may not be sufficient for the treatment of PSC and a combination therapy should be considered.[11] An analogue of UDCA, 2,4-norursodeoxycholic acid (nor-URDA) with a similar mechanism of action of UDCA has demonstrated improvements in rodent models of cholestasis[3] Nor-UDCA has also been evaluated in a recently completed phase 2 clinical trial in 159 patients with PSC.[12]

BBR is an isoquinoline alkaloid found in many different plants, with a long history of use in traditional Chinese medicine.[13, 14] BBR·Cl is an approved antiseptic drug in China, Japan, and Taiwan. In the United States and Australia, BBR is widely used in various dietary supplements for a number of advertised health benefits and is grandfathered under the Dietary Supplement Health and Education Act (DSHEA) in the United States.[15] The reported multi-spectrum activity of BBR, including immunomodulation, anti-inflammation, anti-apoptosis and anti-infection, suggests that BBR has the potential to treat chronic cholestatic liver diseases. Studies show BBR's ability to inhibit the toxic effect of lipopolysaccharide (LPS) and normalize intestinal permeability. Therefore, it is reasonable to believe that BBR may have beneficial effects in the treatment of PSC.

ALP level has been used as a biomarker in clinical trials of PSC for the past two decades and the reduction of ALP has been used as primary endpoint in over 40% of clinical studies.[6, 16-18] ALP was the primary variable used in the FDA's approval of OCALIVA. Recently, several observational studies have further supported the use of ALP as a surrogate marker for transplant-free survival.[19-22] In a phase 2 clinical trial of nor-UDCA in PSC patients, change in serum ALP levels during treatment is used as the primary outcome measure.[23] In a preclinical study by these researchers in a common bile duct ligation induced mice model of cholestasis, the ALP levels were

reduced by approximately 30% after 7-day treatment of nor-UDCA post 3 days of bile duct ligation (BDL).[24] This study will evaluate HTD1801 in adult subjects with PSC by assessing effects of ALP over 6 weeks.

1.1.2 Nonclinical Studies

HighTide conducted an efficacy study of HTD1801 in rats subjected to BDL. HTD1801 at doses of 50 mg/kg and 150 mg/kg reduced ALP levels by 23.8% and 25.1% respectively, increased super oxide dismutase activity, and reduced malondialdehyde levels significantly, providing mechanistic evidence for the action of HTD1801 in the treatment of PSC. In addition, both doses ameliorated hepatocellular necrosis, reduced inflammation in the portal area, and inhibited bile duct proliferation, providing additional evidence of the potential for therapeutic effects of HTD1801 in PSC.

A second pharmacology study was conducted to evaluate the effects of HTD1801 on intestinal microbiota modification in a high-fat diet-induced hamster model of metabolic disorder. Recent clinical observations and animal findings have suggested an abundance of christensenellanceae[25] and decreased parabacteroides[26, 27] have a role in the etiopathogenesis of PSC.

The nonclinical toxicity profiles of both UDCA and BBR have been extensively studied. A full ICH M3 battery of nonclinical studies was performed with UDCA in support of NDA 20675. The toxicity profile of berberine was assessed in a battery on nonclinical studies conducted and/or reviewed by the National Toxicology program. These studies include single dose oral studies in mice and rats, in vitro and in vivo genotoxicity studies, as well as reproductive and developmental toxicity studies in mice and rats.[28-32] The pharmacokinetic and toxicity profile of HTD1801 has been evaluated in both rats and dogs. HighTide conducted toxicology studies of up to 2-weeks in rats (non-GLP) and up to 13-weeks in dogs (GLP). The results of these studies show that combined administration of UDCA and berberine as HTD1801 results in pharmacokinetic and toxicity profiles similar to that of the individual components UDCA and BBR. In addition, the 13-week GLP dog study provided data to qualify the toxicity profile of berberine in nonrodents and the safety of the combination of berberine and UDCA when administered as HTD1801.

1.2 STUDY RATIONALE

This study is a dose ranging, proof-of-concept study with a PK substudy that follows the completion of a single ascending dose study in healthy volunteers.

1.3 DOSE RATIONALE

UDCA was FDA approved at a dose of 13-15 mg/kg/day, which is roughly 1,000 mg UDCA per day. BBR is widely used in dietary supplements in the United States at a recommended dose of 17 to 33 mg/kg/day, which is roughly 1 to 2 g/day. As shown in Table 2, the UDCA and BBR·Cl content of HTD1801 are comparable to that already shown to be safe clinically.

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Table 2. Comparison of HTD1801 Clinical Dose with FDA Approved UDCA Dose and Recommended BBR Cl Dose

Compound	FDA Approved Clinical Dose (UDCA) / Dose used in dietary supplements (BBR-Cl)	HTD1801 Clinical Dose (33 mg/kg/day; 2000 mg/day)[c]
UDCA[a]	13-15 mg/kg/day (780-900 mg/day)[b]	18 mg/kg/day (1078 mg/day)
BBR Cl[a]	17-33 mg/kg/day (1000-2000 mg/day)	17 mg/kg/day (1022 mg/day)

a: mg/kg doses calculated assuming a 60-kg adult
b: Safety at doses up to 25 mg/kg/day is supported by the published literature for PBC patients [33]
c: HTD1801 dose of 2000 mg/day is equivalent to 1022 mg/day BBR Cl and 1078 mg/day of UDCA.

2.0 OBJECTIVES

The primary objective of this proof-of-concept study is to evaluate the effects of HTD1801 on ALP in adult subjects with PSC.

The secondary objectives of this study are to evaluate the effects of HTD1801 on concurrent disease activity of inflammatory bowel disease (IBD), and on the safety and tolerability of HTD1801 over 18 weeks in adult subjects with PSC.

Pharmacokinetic (PK) and pharmacodynamics (PD) objectives include:

- Develop and validate population PK models for the components of HTD1801: berberine (BBR) and ursodeoxycholic acid (UDCA);
- Calculate individual single-dose and steady-state exposure metrics based on non-compartmental analysis methods in adult patients with PSC;
- Evaluate exposure-response models for efficacy;
- Evaluate the relationship between exposure, adverse events, and serious adverse events

3.0 STUDY DESIGN

3.1 BASIC DESIGN CHARACTERISTICS

This proof-of-concept study with a PK substudy will be conducted in three randomized, double-blind treatment periods in adult patients with PSC. The study design consists of an initial randomized, double-blind, placebo- and dose-controlled, parallel group period, followed by a dose-controlled extension period, followed by a placebo-controlled randomized withdrawal period.

- In the 1st period, subjects will be randomized to receive twice-daily doses of 500 mg, 1000 mg, or matching placebo for 6 weeks. The primary analysis will be based on this initial 6 week randomized, double-blind, placebo- and dose-controlled, parallel group period.

- Following the completion of that initial double-blinded, placebo- and dose-controlled parallel group period, subjects will be eligible to enroll in a 6-week extension period in which subjects previously randomized to 500 mg or 1,000 mg twice-daily (BID) will continue for 6 more weeks at that previous dose, while subjects previously randomized to placebo will be re-randomized to receive 6 weeks of either 500 mg or 1,000 mg BID. The study will remain double-blind.

- Following the completion of the 6-week experimental treatment extension, all subjects will be re-randomized to either continue on the active treatment they received in Period 2, or be assigned to placebo. The plan is for 50% of the subjects to remain on the experimental treatment at the previous dose and 50% will receive placebo.

3.2 STUDY POPULATION

Up to 90 patients with PSC will be enrolled as subjects. Eligibility will be established by the investigator on the basis of the inclusion and exclusion criteria. Approximately 36 subjects enrolled at selected sites will undergo additional blood draws for PK/PD analysis.

3.2.1 Inclusion Criteria

To be considered eligible to participate in this study, a subject must meet the inclusion criteria listed below:

1. Male or female between 18 and 75 years of age;

2. Have a clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis;

3. If subjects have Inflammatory Bowel Disease (IBD) they will be eligible to participate. If a subject has IBD, documented evidence of IBD must have been evident by prior endoscopy or in previous medical records for ≥6 months. In addition, subjects may only enter the study with a Partial Mayo Score of 0-4, inclusively. Subjects who are on treatment are allowed, provided they are stable for 3 months if taking:
   i. 5-amino salicylic acid drugs,
   ii. azathioprine,
   iii. 6-mercaptopurine, or methotrexate
   iv. biologics;

4. Have a serum ALP ≥1.5 × upper limit of normal (ULN);

5. Females of child-bearing potential and males participating in the study must either agree to use at least 2 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 3 months after stopping

study drug. Females who are postmenopausal must have appropriate documentation;

6. Be able to understand and sign a written informed consent form (ICF);

7. Subjects receiving allowed concomitant medications need to be on stable therapy for 28 days prior to the Baseline visit, with the exception of UDCA, which should be stable for at least 6 weeks prior to the Baseline visit.

3.2.2 Exclusion Criteria

To be eligible for entry into the study, the subject must not meet any of the exclusion criteria listed below:

1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations;

2. Small duct PSC;

3. Presence of percutaneous drain or bile duct stent;

4. History of cholangiocarcinoma or clinical suspicion of new dominant stricture within 1 year by MRCP/ERCP or clinical judgement. Presence of dominant stricture without ERCP evidence of cholangiocarcinoma is acceptable if stable for ≥ 1 year.;

5. Ascending cholangitis within 60 days prior to Screening;

6. Concomitant overlap syndrome with autoimmune hepatitis (AIH) as diagnosed by AST or ALT > 5x ULN, AND
   i. positive smooth muscle antibody and/or liver-kidney microsomal antibody (LKM), or
   ii. IgG >ULN, or
   iii. Biopsy suggestive for AIH

7. Concomitant overlap syndrome with primary biliary cholangitis (PBC) as diagnosed by either:
   i. positive AMA or
   ii. biopsy suggestive for PBC
8. **History of alcohol or substance abuse or dependence**;
9. Prior or planned liver transplantation;
10. Presence of alternative causes of chronic liver disease, including alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis;
11. Platelet count below 125,000/mm^3, albumin below 3.0 g/dL, International Normalized Ratio (INR) > 1.2, or a history of ascites, or encephalopathy, or history of esophageal variceal bleeding;
12. Anticoagulant therapy, with the exception of acetylsalicylic acid;
13. Severe active IBD or flare in colitis activity within the last 90 days requiring intensification of therapy beyond baseline treatment;
14. Use of oral prednisone/prednisolone > 10 mg/day;
15. Hospitalization for colitis within 90 days;
16. AST > 5 x ULN;
17. ALT > 5 x ULN;
18. Total bilirubin > **1.2 x** ULN. **If total bilirubin result at screening is > ULN but ≤ 1.2 x ULN, a confirmatory total bilirubin should be collected after 21 days. If the confirmatory total bilirubin remains ≤ 1.2 x ULN, and all other eligibility criteria continue to be met, the subject will be eligible.**;
19. Evidence of Gilbert's Syndrome;
20. Immunoglobulin G4 (IgG4) > 2 × ULN at screening or evidence of IgG4-related sclerosing cholangitis;

21. **Estimated glomerular filtration rate (eGFR) < 60mL/min/1.73m^2, calculated by the local laboratory;**

22. Hemoglobin < 10 g/dL for males or females;

23. Hepatitis B surface antigen positive;

24. Hepatitis C antibody positive;

25. Human immunodeficiency virus (HIV)-1 or HIV-2 infection;

26. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.

27. History of malignancy within the past 2 years or ongoing malignancy other than basal cell carcinoma, or resected noninvasive cutaneous squamous cell carcinoma;

28. Active, serious infections that require parenteral antibiotic or antifungal therapy within 30 days prior to Screening;

29. Major surgical procedure within 30 days of Screening or prior organ transplantation;

30. Females who are pregnant or breastfeeding;

31. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents and immune-modulating agents (such as systemic corticosteroids, interleukins, interferons);

32. Allergy to the clinical trial material or its components;

33. Received any experimental medications within 30 days prior to Screening;

34. 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.

3.3 ENDPOINTS

3.3.1 Efficacy

3.3.1.1 Primary Endpoint

The primary endpoint for this study is the change in serum alkaline phosphatase between Baseline and Week 6.

3.3.1.2 Secondary Endpoints

The secondary endpoints of this study include the following:

1. Change in serum ALP between Baseline and Weeks 12 or 18, dependent upon the length of continuous treatment, compared to the placebo response during Period 1;

2. Change in serum ALP between a new baseline at Week 6 and the final value at Weeks 12 for those subjects who received placebo during Period 1, compared to their initial 6-week placebo response;

3. Change in serum ALP between a new baseline at Week 6 and the final value at Weeks 12 for those subjects who received placebo during Period 1, compared to the similar change in the 500 mg and 1,000 mg treatment groups;

4. Change in serum ALP between a new baseline at Week 12 and the final value at Weeks 18 for all subjects following the randomized withdrawal;

5. Proportion of patients who achieve ALP of <1.5 x ULN;

6. Proportion of patients who achieve a 50% decrease in ALP;

7. The proportion of patients who normalize ALP;

8. Change in AST/ALT ratio;

9. Change in serum bilirubin;

10. In subjects with IBD who have elevated fecal calprotectin (FC), change in FC compared to Baseline at Weeks 6 and 12, and the proportion of subjects who normalize FC at Weeks 6 and 12;

11. For subjects who have elevated CRP at Baseline (for all subjects In the IBD subset): change from Baseline in CRP at Weeks 6 and 12, and normalization of CRP at Weeks 6 and 12.

12. For subjects with IBD who have Partial Mayo score above 0: Change from Baseline in Mayo scores at Weeks 6 and 12.

3.3.2 Safety

Safety endpoints to be used in this study will include:

1. Proportion of subjects with a treatment-emergent adverse event (TEAE) or a clinically significant laboratory abnormality (overall and of any given type);
2. Proportion of subjects who discontinue due to an adverse event (AE) (either treatment-emergent or clinically significant laboratory abnormality).

3.3.3 Pharmacokinetic Endpoints

1. Apparent clearance (CL/F) of UDCA and BBR;
2. Apparent volume of distribution at steady state (Vss/F) for UDCA and BBR;
3. Additional single-dose and steady-state non-compartmental exposure metrics (e.g., C_{max}, AUC_{0-12}, AUC_{0-inf}).

3.4 RANDOMIZATION AND BLINDING

Period 1: Placebo- and dose-controlled, parallel-group period

Subjects will be enrolled in equal numbers to one of the initial three treatment groups, those being placebo BID, HTD1801 500 mg BID, or HTD1801 1,000 mg BID, during the initial 6-week, double-blind, placebo- and dose-controlled, parallel-group period. Randomization will be centrally controlled, stratified according to a co-existing diagnosis of IBD, and subjects will be assigned a pre-packaged and numbered treatment.

Period 2: Dose-controlled extension

Following their completion of Period 1, subjects will enroll in a 6-week extension period in which subjects previously randomized to 500 mg or 1,000 mg BID will continue for 6 more weeks at that previous dose, while subjects previously randomized to placebo will be randomly assigned to receive 6 weeks of either 500 mg or 1,000 mg BID.

Period 3: Randomized withdrawal

Following their completion of Period 2, subjects will enroll in a 6-week randomized withdrawal period in which all subjects will be randomly assigned to either continue on the active treatment they received in Period 2, or be assigned to placebo. The plan is for 50% of the subjects to remain on the experimental treatment at the previous dose, and 50% will receive placebo.

All subjects and study personnel (other than an unblinded statistician who will develop the randomization number list, and an unblinded EDC designer will load the randomization number list into the EDC system) will remain blinded as to the treatment administered throughout the study. All study test article will be provided in matching white tablets, four to a bottle, two bottles to be administered each day, one in the morning and one in the evening. A 45-day supply will be provided to each subject at each visit to cover the next 6-week period with an additional 3-days of coverage to provide for possible scheduling conflicts.

In this double-blind study, if a medical emergency occurs and a decision about a subject's condition requires knowledge of the treatment assignment in order to properly treat the subject, the study blind may be broken for that specific subject only. Ideally, this decision to break the blind for this one subject should only be made after consultation with the Medical Monitor or Sponsor Representative.

Any broken blind must be clearly justified and explained by a note in the subject's source documents.

3.5 REPLACEMENT OF DROPOUTS

Subjects who do not complete study assessments through Week 6 of the initial double-blind period are eligible to be replaced at the Sponsor's discretion.

4.0 DRUGS AND DOSAGES

4.1 IDENTIFICATION AND DESCRIPTION OF INVESTIGATIONAL PRODUCT

4.1.1 Investigational Product

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. HTD1801 is expected to dissociate into BBR·Cl and UDCA after oral administration.

4.1.2 Labeling

The study medication and placebo will be supplied by HighTide and packaged into white polyethylene bottles, induction--sealed with aluminum foil and a polyethylene bottle gap. Each bottle will contain 4 tablets and be affixed with a single-panel label that will describe the following information: protocol number, study medication, dose, kit number, sponsor name, instructions for storage between 35.6°F and 46.4°F (2°C and 8°C), and includes the statement "Caution: New Drug - Limited by or United States law to investigational use."

A 3-month supply of bottles will be placed into kits packaged for weekly use, and each patient will receive the appropriate number of kits to provide supplies until their next scheduled visit to the investigational site. Each kit will bear a label describing the following information: study medication, dose, kit number, protocol number, instructions for storage between 35.6°F and 46.4°F (2°C and 8°C), instructions for use, the sponsor name, and the includes the statement "Caution: New Drug - Limited by United States law to investigational use."

4.2 DOSING INSTRUCTIONS AND SCHEDULE

Subjects are instructed to take the entire contents of one bottle of study medication each morning and each evening with water and food. Each bottle will contain four identical white tablets. Subjects should retain the empty bottles and return them to the study site on their next visit along with any unused study medication.

4.3 HANDLING OF INVESTIGATIONAL PRODUCT

The Investigator will be fully responsible for the security, accessibility and storage of the test articles while they are at the investigational site. The Investigator is also responsible for the education of study staff in the correct administration of the test articles.

4.4 COMPLIANCE WITH INVESTIGATIONAL PRODUCT

Subjects will be queried about their compliance and the number of full and empty study medication bottles will be captured on the CRF.

4.5 CONCOMITANT MEDICATIONS

Any non-prohibited concomitant medications are to be continued during the study at the same dosage strength and frequency, and should not be taken within 1 hr prior to dosing or up to 6 hrs following dosing. Changes to concomitant medications are not to be made unless medically necessary. The need for the change must be documented, e.g., in response to an AE.

Patients should be cautioned about the use of glucose lowering drugs. The berberine component of HTD1801 is reported to lower blood glucose and may potentially cause hypoglycemia in patient taking other glucose lowering drugs at the same time. Patients who take glucose lowering drugs should be already aware of the most common symptoms of low blood sugar (dizziness, sweating, unusual hunger, shakiness, and a very rapid heartbeat) and should know how to react; in all these cases, however, patients should report these events to the Investigator.

4.6 PROHIBITED CONCOMITANT MEDICATIONS

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. These exclusions are primarily due to the currently unknown drug interaction profile of the berberine component of HTD1801. Medications known to be strong inhibitors of P-glycoprotein (P-gp), CYP3A4, and CYP2D6, and p-gp substrates with a narrow therapeutic index are excluded, as shown in Table 3 below:

Table 3. Prohibited Medications

P-glycoprotein	CYP3A4	CYP2D6
clarithromycin	clarithromycin	bupropion
amiodarone	telithromycin	fluoxetine
erythromycin	nefazodone	fluoxamine
ketoconazole	itraconazole	quinidine
quinidine	ketoconazole	terbinafine
saquinavir	atazanavir	
verapamil	darunavir	
	indinavir	
digitalis	lopinavir	
lovastatin	nelfinavir	
sildenafil	ritonavir	
	saquinavir	
	tipranavir	
	chloramphenicol	
	cobicistat	
	grapefruit juice	

Source:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2

5.0 EXPERIMENTAL PROCEDURES

5.1 PROCEDURES, MEASUREMENTS AND EVALUATIONS

Study procedures are summarized across all study visits as indicated in the Study Design (Figure 1), Pharmacokinetic Substudy Design (Figure 1PK), and the Schedule of Time and Events (Table 1).

Throughout the study, blood and urine samples will be collected in a fasting state. Study medication should be taken with water and food.

5.1.1 Screening (Days -28 to 0)

Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. Subjects who are currently taking UDCA, or who have taken UDCA during the past 6 weeks, must have been receiving a stable dosage regimen for at least 6 weeks before Baseline measurements can be taken (see Section 5.1.2 below). Screening is to occur no more than 28 days before the Baseline visit. Potential subjects who do not meet all eligibility criteria at Screening will be allowed to rescreen once. If a potential subject fails to meet eligibility criteria upon rescreen, he or she will remain ineligible for the study.

During Screening, the following procedures must be conducted and assessments obtained. The information will be collected in a source document templates provided by the Sponsor. Local laboratories may be used for all blood and urine samples collected for purposes of Screening.

- Informed consent
- Confirm eligibility criteria
- Demographic information
- Medical History
- Physical Examination
- Weight, height
- Vital signs

- Prior and concomitant medications
- Glucose-6-phosphate dehydrogenase (G6PD)
- Electrocardiogram, 12 lead (ECG)
- Urine drug test
- HIV, and Hepatitis B, C
- Pregnancy test (urine or serum)
- Complete Blood Count (CBC),
- Comprehensive Metabolic Panel (CMP) that includes ALP, AST, ALT, bilirubin

  If total bilirubin result at Screening is > ULN but ≤ 1.2 x ULN, a confirmatory total bilirubin should be collected after 21 days. If the confirmatory total bilirubin remains ≤ 1.2 x ULN, and all other eligibility criteria continue to be met, the subject will be eligible.
- INR
- Serum IgG4 if no evidence of IgG4-related sclerosing cholangitis.
- Partial Mayo Score **(see Appendix D)**

Subjects will be instructed to stop all prohibited medications (see Section 4.6) prior to beginning Baseline procedures.

5.1.2 Baseline (immediately prior to dosing)

Potential subjects who have successfully completed all of the Screening procedures and have met all the eligibility criteria (see Sections 3.2.1 and 3.2.2) will be eligible for enrollment in the study. Prior to randomization, potential subjects will undergo the following Baseline procedures and assessments:

- An update of Medical History information
- Physical examination and vital signs
- An update of prior and concomitant medications
- ECG
- Confirmation of non-pregnant status for females

If the potential subject continues to satisfy the Inclusion/Exclusion criteria based upon these procedures and assessments stated above, those data will become part of the Baseline. Those potential subjects may be randomized and officially become subjects in the study. **Subjects who have been taking UDCA will be instructed to discontinue UDCA prior to the Baseline visit.** Subjects will again be instructed to avoid any use of the prohibited medications listed in Section 4.6 for the entire duration of the study, or until formally instructed otherwise.

Patients should also be cautioned about the use of glucose lowering drugs. The berberine component of HTD1801 is reported to lower blood glucose and may potentially cause hypoglycemia in patient taking other glucose lowering drugs at the same time. Patients who take glucose lowering drugs should be already aware of the most common symptoms of low blood sugar (dizziness, sweating, unusual hunger, shakiness, and a very rapid heartbeat) and should know how to react; in all these cases, however, patients should report these events to the Investigator.

Prior to dosing on Visit 2, the following additional Baseline procedures and assessments are to be conducted at the investigational site. All clinical laboratory samples are to be sent to the designated central laboratory for analysis. These Baseline central laboratory data will not be used to determine eligibility in the study as the newly enrolled subject has already been randomized. The additional pre-dose Baseline procedures are to include:

- CBC
- INR
- CMP that includes ALP, AST, ALT, bilirubin
- Standard serum lipid panel
- Partial Mayo Score
- Mayo Risk Score
- Plasma C-reactive protein(CRP) (only in patients with IBD)
- Stool sample for fecal calprotectin (FC) (only in patients with IBD). The stool sample testing may be completed separately from the site visit.

For subjects participating in the PK substudy, additional blood samples for PK analysis will be collected, processed, and sent to the designated central laboratory. PK samples will be collected at the following timepoints (see Table 1PK):

- Pre-dose
- 1, 2, 3, 4, 6, and 8 hours post-dose

Subjects participating in the PK substudy will be required to maintain a dosing diary. The date and time of each dose of study medication taken on the last 3 days prior to the Week 6 visit must be recorded, and the diary must be brought back to the site at the Week 6 clinic visit.

Following the successful completion of all Baseline procedures, the subject will self-administer the first dose of the study medication, consisting of 4 tablets, under the supervision of study personnel. The subject will be provided an entire 6-week supply of study medication consisting of a total of 90 dosage units, each containing 4 tables. The subject will be instructed to swallow the contents of one dosage unit containing 4 tablets in the morning, and one dosage unit containing 4 tablets in the evening, each day until they return to the investigational site 6 weeks later for the next visit. Subjects will be instructed to contact the investigational site immediately if any problems or concerns arise.

5.1.3 Double-Blind Treatment Period - Weeks 2, 4, and 6

During the double-blind treatment period, the following procedures and assessments will be conducted on Weeks 2 and 4:

- Subjects are required to provide blood samples for CBC, CMP, and Lipids. This will not require a visit to the study site and will involve local sample collection.
- Subjects will be contacted by the Investigator, or one of their staff, to discuss the occurrence of any AEs, any new or changes in concomitant medications, adherence to the treatment schedule, and compliance with the requirement to visit a pre-specified clinical laboratory for CBC, CMP, and Lipids. Any new medications that are being taken are, by default, to be considered as being necessitated by an AE. If necessary, subjects may be asked to visit the investigational site, at the Investigator's discretion.

- It is recognized that some investigational sites may require subjects to come to the clinic for these visits and related activities.

During the double-blind treatment period, the following procedures and assessments will be conducted during the visit to the investigational site on Weeks 6:

- Prior and concomitant medications will be reviewed and any changes will be recorded on the appropriate eCRF page. Generally, any new medications that are being taken are, by default, to be considered as being necessitated by an AE. Rarely, a previously unmentioned prior medication may be disclosed, and that eCRF page should be updated.
- A physical examination including vital signs will be conducted and any findings that represent clinical deteriorations from Baseline are to be recorded as Adverse Events.
- An ECG is to be recorded. Any findings that represent clinical deteriorations from Baseline are to be recorded as an AE.
- Blood samples for CBC, INR, CMP, and Lipids panel are to be collected and sent to the designated central laboratory. Any subsequent findings that represent clinical deteriorations from Baseline are to be recorded as an AE.
- Partial Mayo Score.
- Subjects with IBD will provide a blood sample for C-reactive protein.
- Subjects with IBD will also complete a test for fecal calprotectin. (The stool sample testing may be completed separately from the site visit.)
- The subject is to be queried for any changes to existing AEs, or any additional AEs that may have occurred during the intervening period.

After the Week 6 visit, all subjects are eligible to enroll into the 6-week Dose-controlled Extension Period of the study. Subjects who do not wish to continue may choose to discontinue and should be handled according to the information listed in Sections 5.1.6 and Section 7.0.

For subjects participating in the PK substudy and continuing into the Dose-controlled Extension Period, the subject will be instructed not to take the morning dose of study medication at home on the day of the Week 6 visit. The morning dose will be taken in

the clinic, the dosing diary will be collected, and additional blood samples for PK analysis will be collected, processed, and sent to the designated central laboratory. PK samples will be collected at the following timepoints on Week 6 (see Table 1PK):

- Pre-dose (taken in clinic)
- 1, 2, 3, 4, 6, and 8 hours post-dose

PK samples will not be collected during the Week 6 visit for subjects who withdraw from the study prior to beginning the Dose-controlled Extension Period.

5.1.4 Dose-controlled Extension Period - Weeks 8, 10, and 12

During the dose-controlled extension period, the following procedures and assessments will be conducted at Weeks 8 and 10:

- Subjects are required to provide blood samples for CBC, CMP, and Lipids. This will not require a visit to the study site and will involve local sample collection.
- Subjects will be contacted by the Investigator, or one of their staff, to discuss the occurrence of any AEs, any new or changes in concomitant medications, adherence to the treatment schedule, and compliance with the requirement to visit a pre-specified clinical laboratory for CBC, CMP, and Lipids. Any new medications that are being taken are, by default, to be considered as being necessitated by an AE. If necessary, subjects may be asked to visit the investigational site, at the Investigator's discretion.
- It is recognized that some investigational sites may require subjects to come to the clinic for these visits and related activities.

During the dose-controlled extension period, the following procedures and assessments will be conducted during the visit to the investigational site on Weeks 12:

- Prior and concomitant medications will be reviewed and any changes will be recorded on the appropriate eCRF page. Generally, any new medications that are being taken are, by default, to be considered as being necessitated by an Adverse Event. Rarely, a previously unmentioned prior medication may be disclosed, and that eCRF page should be updated.

- A physical examination including vital signs will be conducted and any findings that represent clinical deteriorations from Baseline are to be recorded as Adverse Events.
- An ECG is to be recorded. Any findings that represent clinical deteriorations from Baseline are to be recorded as an AE.
- Blood samples for CBC, INR, CMP, and Lipids panel are to be collected and sent to the designated central laboratory. Any subsequent findings that represent clinical deteriorations from Baseline are to be recorded as an AE.
- Partial Mayo Score.
- Subjects with IBD will provide a blood sample for C-reactive protein.
- Subjects with IBD will also complete a test for fecal calprotectin. (The stool sample testing may be completed separately from the site visit.)
- The subject is to be queried for any changes to existing AEs, or any additional AEs that may have occurred during the intervening period.

After the Week 12 visit, all subjects are eligible to enroll into the 6-week Randomized Withdrawal Period of the study. Subjects who do not wish to continue may choose to discontinue and should be handled according to the information listed in Sections 5.1.6 and Section 7.0.

5.1.5 Random Withdrawal Period, Weeks 14, 16, and 18

During the random withdrawal period, the following procedures and assessments will be conducted on Weeks 14 and 16:

- Subjects are required to provide blood samples for CBC, CMP, and Lipids. This will not require a visit to the study site and will involve local sample collection.
- Subjects will be contacted by the Investigator, or one of their staff, to discuss the occurrence of any AEs, any new or changes in concomitant medications, adherence to the treatment schedule, and compliance with the requirement to visit a pre-specified clinical laboratory for CBC, CMP, and Lipids. Any new medications that are being taken are, by default, to be considered as being necessitated by an AE. If necessary, subjects may be asked to visit the investigational site, at the Investigator's discretion.

- It is recognized that some investigational sites may require subjects to come to the clinic for these visits and related activities.

During the random withdrawal period, the following procedures and assessments will be conducted during the visit to the investigational site on Weeks 18:

- Prior and concomitant medications will be reviewed and any changes will be recorded on the appropriate eCRF page. Generally, any new medications that are being taken are, by default, to be considered as being necessitated by an Adverse Event. Rarely, a previously unmentioned prior medication may be disclosed, and that eCRF page should be updated.
- A physical examination including vital signs will be conducted and any findings that represent clinical deteriorations from Baseline are to be recorded as Adverse Events.
- An ECG is to be recorded. Any findings that represent clinical deteriorations from Baseline are to be recorded as an AE.
- Blood samples for CBC, INR, CMP, and Lipids panel are to be collected and sent to the designated central laboratory. Any subsequent findings that represent clinical deteriorations from Baseline are to be recorded as an AE.
- Partial Mayo Score.
- Subjects with IBD will provide a blood sample for C-reactive protein.
- Subjects with IBD will also complete a test for fecal calprotectin. (The stool sample testing may be completed separately from the site visit.)
- The subject is to be queried for any changes to existing AEs, or any additional AEs that may have occurred during the intervening period.

5.1.6 Study Discharge

Following the successful completion of all procedures at the Week 18 visit, all subjects are to undergo discharge procedures. This will include instructions to the subject to contact the investigational site immediately if any problems or concerns arise during the next 4 weeks of follow-up. Female subjects will complete a pregnancy test. Pregnancy is not to be recorded as an Adverse Event.

5.1.7 Follow-up Period (Week 22)

Subjects will undergo follow-up evaluations 4 weeks after the last dose of study drug. The follow-up can be via phone, providing the patient has no health concerns related to the study. The subject may be asked to return to the investigational site if the Investigator thinks it is advisable for safety reasons. The following assessments will be conducted by phone or other contact at Week 22:

- AE monitoring
- Concomitant medications (query for any possible relationship to an AE)

Following the completion of the follow-up procedures, the subject is officially discharged from the study.

6.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.1 DEFINITION OF AN ADVERSE EVENT

The following definition of adverse event (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.

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 preexisting 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

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

AEs 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 study staff will note all AEs mentioned by the subject at Baseline and during administration of the investigational product. All clinical complaints volunteered by or elicited from the subject during the study will be recorded on the appropriate page of the electronic case report form (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 annual report or more frequently if requested by the regulatory agency. SAEs require special reporting in addition to documentation in the eCRF as described in Section 6.7.

6.2 DEFINITION OF A SERIOUS ADVERSE EVENT

In this study, a serious adverse event 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.
- An 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).

6.3 RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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.

6.4 ASSESSMENT OF INTENSITY

The investigator will assess the intensity for each AE and SAE reported during the study on the basis of his or her clinical judgement. The classifications in Table 4 should be used in assigning intensity of each AE recorded in the case report form.

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Table 4. Classification of AEs by Intensity[a]

Intensity	Definition
Mild AE (Grade 1)	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
Moderate AE (Grade 2)	An event that is sufficiently discomforting to the extent of interfering with normal everyday activities
Severe AE (Grade 3)	An event that prevents the subject from performing normal everyday activities
Life-threatening or disabling AE (Grade 4)	An event that, at the time of occurrence, put the subject at risk of death or resulted in a persistent or significantly disability or incapacity
Death related to AE (Grade 5)	An event that resulted in death

AE = adverse event
a From Common Terminology Criteria for Adverse Events, version 4.0

Any AE that changes in intensity 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, 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 6.1.

6.5 ASSESSMENT OF CAUSALITY

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

one of the criteria 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.

AE = adverse event.

6.6 EXPECTEDNESS OF SERIOUS ADVERSE EVENTS

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.

6.7 REPORTING OF SERIOUS ADVERSE EVENTS

1. Any SAE occurring after the subject signs the informed consent form and the investigational product has been administered, as described in Section 6.1, must be reported to the Medical Monitor 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 competed 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

SAE = serious adverse event.

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 pharmacovigilance within the designated time frames. If additional information to complete the SAE report is needed, the investigator will not wait before notifying the safety department of the SAE. The SAE report will be updated by the investigator when additional information is received.

6.8 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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.

The appropriate SAE report will be updated once the SAE resolves, stabilizes, or is otherwise explained or until the subject is lost to follow-up. The investigator will also ensure that updates include any supplemental data that may explain causality of the SAE(s).

New or updated information will be recorded on a copy of the initial SAE report form; all incorrect data should be marked out (by a single line), initialed, and dated by the investigator or designee, with the new information clearly recorded. The updated SAE report form will then be signed and dated by the investigator and resubmitted to the pharmacovigilance department as outlined in Table 6.

6.9 LIVER ADVERSE EVENTS

The following algorithm will be used to monitor for drug-induced liver injury (DILI):

If isolated transaminase (AST or ALT) elevations are observed, defined as: Normal bilirubin and absence of clinical hepatitis, AND

1. ALT or AST ≥ 5 times the ULN if normal at baseline, OR
2. ALT or AST ≥ 3 times the baseline or ≥ 400 U/L if abnormal at baseline

Then

1. Repeat liver profile (ALT, AST, bilirubin and PT/INR) within 2 to 3 days, AND
2. Monitor the patient with laboratory testing and physical examination 2 to 3 times per week as per the "close observation" definition in the DILI guidance (https://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf).

If any ONE of the following criteria is met:

- Transaminases (ALT or AST ≥ 3 x baseline) AND bilirubin (total bilruibin > 2 x ULN), OR
- Cholestatic markers (ALP or GGT > 2 x baseline), OR
- Isolated ALT/AST ≥ 8x ULN or 600 U/L in the presence of normal CPK and LDH and not secondary to cholangitis, OR
- INR increase > 1.5 refractory to vitamin K administration

OR: if any ONE of the following criteria is met for total bilirubin unrelated to hemolysis:

1. Doubling of total bilirubin
   - OR: any increase in total bilirubin if there are symptoms of clinical hepatitis (e.g., vomiting, nausea, right upper quadrant pain),
   - OR: there are immunological reactions (rash or >5% eosinophilia),

Then

1. study medication must be interrupted, and
2. a drug-induced liver injury workup must be initiated for alternate etiologies;
3. repeat a liver profile (ALT, AST, total bilirubin, direct bilirubin, ALP) and PT/INR within 48 to 72 hours;
4. monitor the patient with further laboratory testing and physical examination 2 to 3 times per week as per the "close observation" definition in the DILI guidance (https://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf.
5. If a subject lives in a remote area, they can be tested locally and the results communicated to the investigator promptly.

Rechallenge

1. Only if a firm alternate etiology is identified AND liver tests have returned to baseline (a rechallenge may be considered)
2. If cholangitis is the etiology – diagnosis must be firmly established according to the protocol definition before a rechallenge is considered

Rechallenge is not recommended if it is determined that the subject has had a drug induced liver injury.

6.10 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.

7.0 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

7.1 ADVERSE EVENT STOPPING RULES

If a subject experiences an AE that, in the judgment of the investigator, the sponsor, or the medical monitor, presents an unacceptable consequence or risk to the subject, the subject may be discontinued from the study.

If a participant develops cholangitis or an inflammatory bowel disease (IBD) flare twice during the trial, then the patient should be discontinued from study drug, but maintained in the study for safety follow-up.

- Cholangitis is defined as cholestasis and systemic inflammation demonstrated by clinical signs or blood test results in addition to biliary manifestations demonstrated by imaging.

- Inflammatory bowel disease flare-ups are defined as unexpectedly frequent and/or urgent bowel movements, diarrhea, bloody stools or abdominal pain, not requiring systemic immunosupression with a corticosteroid or a biological agent.

If a participant develops a dominant stricture or an IBD flare requiring new or increased of immunosupressive therapy (systemic corticosteroids or biologics), then the patient should be discontinued from study drug, but maintained in the study for safety follow-up.

- A dominant stricture is defined as intervention due to symptoms, compelling imaging results, or a prominent increase in liver biochemical markers.

7.2 NONCOMPLIANCE

After the investigator, the medical monitor, or study monitor consult (and the sponsor if appropriate), a subject may be discontinued from the study for the following administrative reasons:

- Failure to receive study medication or treatment as mandated by the instructions provided in Section 4.0

- Failure to comply with protocol requirements

- Unauthorized, subject-initiated changes in dosing regimen

7.3 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. Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator will provide a written explanation of the reason for discontinuation in a source document and this information will be recorded on the appropriate eCRF page. Subjects will be specifically queried to determine whether or not withdrawal of consent might have been due to an adverse event. If a subject withdraws before completion, every effort should be made to complete the assessments scheduled during the follow-up period [termination/end of study visit]. A subject may be removed from the study for the reasons described in Section 7.1 through Section 7.3.

7.4 PREMATURE STUDY OR SITE TERMINATION

If the sponsor, investigator, medical monitor, study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the site should be terminated, this action may be taken after appropriate consultation among the sponsor, investigator, medical monitor, and study monitor. The Common Terminology Criteria for Adverse Events (CTCAE) will be used to for the assessment of trial stopping criteria.

The study trial will be stopped if:

- Three patients develop the same Grade 3 CTCAE
- OR: Two patients develop any Grade 4 CTCAE
- OR: One patient develops a Grade 5 CTCAE

Additional conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product

A study conducted at a single site in a multicenter study may also warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate
- Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the site to the sponsor, study monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will comply with the conditions set forth in International Council for Harmonisation E6, Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

8.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

8.1 DATA COLLECTION AND PROCESSING

Electronic case report forms (eCRFs) will be used to capture study assessments and data. The study coordinator or other delegated study staff will enter data from source documents into the eCRFs. All eCRFs will be reviewed and source-verified by the study monitor during periodic site visits, and the study monitor will ensure that all data in the eCRF are correct and complete. Before or between visits, the medical monitor or study monitor may conduct a preliminary medical review of the eCRFs. Once the eCRFs are completed and source-verified, the investigator must electronically sign all required eCRF pages, verifying the accuracy of all data contained in the eCRFs.

Training will be provided for the electronic data capture (EDC) system. All study staff using the EDC system must have the necessary education, training, and experience or any combination of these. The investigator will be responsible for documenting employee education, training, and previous experience that pertain to the EDC system for all site staff using the EDC system.

The investigator must maintain adequate security of the EDC system, including documentation that all users have been trained on the appropriate standard operating procedure and a list of authorized users. To ensure all data entries can be tracked, all personnel responsible for data entry must obtain a unique user identification (user ID) and password before any data can be entered in the eCRFs. Authorized study staff will be assigned a unique user ID only after receiving standard operating procedure training.

If electronic data systems other than those provided and maintained by the sponsor are used for documentation and data capture, the investigator must ensure that the systems are validated and that data are backed up as described in Section 9.2.

8.2 STATISTICAL ANALYSIS

8.2.1 General Overview

The data will be summarized in tables by treatment period and treatment group, as appropriate, showing the number of subjects with nonmissing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. Data will also be listed as deemed appropriate. All statistical analyses will be performed and data appendices will be created by using SAS version 9.4 or later.

All statistical tests will be two-sided with an alpha (α) level of 0.05.

8.2.2 Populations of Interest

The modified Intent-to-treat population (mITT) will consist of all randomized subjects who receive at least one dose of study drug and who have at least one post-dose efficacy assessment.

The safety population will include randomized subjects who receive at least one dose of study drug.

8.2.3 Efficacy Analysis

The mITT population will be used for the analysis of all efficacy endpoints. No alpha adjustments for multiplicity will be made for the analysis of efficacy endpoints for this proof of concept study.

The primary efficacy variable is the change in ALP from Baseline to Week 6 in the double-blind parallel group period. Changes in ALP from Baseline will be summarized by treatment group and visit using descriptive statistics. A mixed model repeated measures (MMRM) will be fit to the data and the model will include fixed factors for treatment, randomization strata of IBD diagnosis, visit and treatment by visit interaction, and Baseline value as a covariate. An unstructured covariance matrix will be used to model the repeated assessment over time. Denominator degrees of freedom will be adjusted using Kenward-Roger's method. Sensitivity analyses will be described in the statistical analysis plan (SAP). Treatment comparisons will be made at each visit,

with the primary comparison at Week 6. No imputation of missing data is necessary for the MMRM analysis of the primary endpoint. A similar MMRM analysis will be performed for the randomized withdrawal period. Analysis for the randomized withdrawal period will be conducted for all subjects and separately for responders based on pre-specified responder criteria. For the dose-controlled treatment period, a one sample t-test will be used to evaluate the change in ALP from Week 6 to Week 12 for the subjects who were previously randomized to placebo during the first period.

The secondary efficacy variables of the proportion of subjects who normalize ALP, the proportion of subjects who achieve ALP of < 1.5 x ULN and the proportion of subjects who achieve a 50% decrease in ALP from Baseline will be calculated at the end of treatment using a last observation carried forward for any missing data. Frequencies and percentages will be calculated by treatment group and by visit. Any adjustments for multiplicity will be discussed in the SAP. Treatment comparisons will be made at Week 6 (or LOCF) using Fisher's exact test. A similar analysis will be performed for the randomized withdrawal period. For the dose-controlled extension period, a one sample exact test will be used to evaluate the proportion of subjects achieving each of the secondary endpoints at Week 12 for the subjects who were randomized to placebo during the first double-blind period. The secondary efficacy variables of change from Baseline in AST/ALT ratio, bilirubin, and IgG4 will be analyzed using a MMRM similar to that described above for the primary efficacy variable.

Further details of the efficacy analyses will be provided in a separate statistical analysis plan.

8.2.4 Safety Analysis

The safety population will be used for all safety analyses. AE data will be listed individually, and the incidence of adverse events will be summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE will be counted only once for a given subject within a specified system organ class, preferred term. If the same AEvent occurs on multiple occasions for a subject, the occurrence with the highest severity and relationship to study drug will be reported. If two or more AEs are reported as a unit, the individual terms will be reported as separate events.

Changes in vital signs, hematology, and clinical chemistry parameters from Baseline to the end of the study will be examined. Treatment-emergent changes from normal values to abnormal values in key laboratory parameters will be identified.

8.2.5 Pharmacokinetic Analysis

Population PK models for the components of HTD1801 (UDCA and BBR) will be developed and validated using a nonlinear mixed-effects model (NONMEM) approach. The model for UDCA will include endogenous UDCA. The error model will include between-subject variability and residual error between observed and predicted concentration (using NONMEM's FOCE method). Selection of the appropriate model will be based on hypothesis testing using the likelihood ratio test and graphical analysis of residual error (goodness of fit). Target parameters for each component include apparent clearance (CL/F) and apparent volume of distribution at steady state (V_{ss}/F). Covariate relationships between PK parameters and individual characteristics will be evaluated and incorporated into the model as indicated by the data. Covariates for evaluation will include, but will not be limited to, vital signs (e.g.,, body size), demographics (e.g., sex, age, race) and organ function / disease biomarkers (e.g., bilirubin and alkaline phosphatase). The models will be validated using likelihood profiles, bootstrap analysis, and visual predictive check.

Concentration vs. time profiles will be simulated for each subject based on that subject's individual-specific (post-hoc) parameter estimates. Individual single-dose and steady-state non-compartmental metrics will be calculated from this simulated data (e.g., C_{max}, $AUC_{0\text{-}12}$, $AUC_{0\text{-}inf}$). Metrics for UDCA will be reported with and without baseline correction.

8.2.6 Pharmacokinetic/Pharmacodynamic Analysis

An exploratory exposure-response analysis will be performed to evaluate the relationship between exposure metrics (e.g., AUC, C_{max}) for UDCA, BBR, and UDCA+BBR and change from baseline in serum ALP. The analysis will evaluate the effect of covariates including disease state (e.g., baseline ALP; IBD with elevated FC; elevated CRP).

An exploratory exposure-response analysis will be performed to evaluate the relationship between exposure, adverse events (AE) of interest, and serious adverse

events (SAE). The relationship between exposure and AE or SAE occurrence will be evaluated graphically and, where indicated, statistically.

8.2.7 Sample Size

Results from published clinical trials of PSC patients including Zhu et al., 2015 and Fickert et al., 2017 were reviewed.[10, 34] These publications were used along with consideration of inclusion and exclusion criteria for this study to estimate mean baseline ALP and to estimate variability. Total sample size was chosen based on balancing consideration of business costs, time to enroll subjects with this rare disease and the mean change which could be detected given the mean baseline and variability assumptions. The standard deviation for change from baseline in ALP was assumed to be 200. A total of 90 subjects, 30 subjects per group is sufficient to detect a mean difference from placebo within a dose group of 147 with 80% power at an alpha of 0.05. Assuming a mean baseline ALP of 450, this equates to a 32.7% reduction. This study whould be adequate to determine if there is a positive signal in ALP during HTD1801 treatment.

No formal sample size analysis was performed for the PK substudy. Thirty-six (36) subjects providing up to 504 pharmacokinetic samples is considered sufficient to characterize CL/F and V_{ss}/F of UDCA and BBR in this study population.

9.0 STUDY ADMINISTRATION

9.1 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 period evaluations. One copy of the signed informed consent form 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 informed consent form and authorization for use and disclosure of protected health information, which is prepared by the investigator or the study 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 informed consent form must contain the 20 elements of informed consent described in International Council for Harmonisation 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.

9.2 STUDY DOCUMENTATION

9.2.1 Investigator Information

Investigator information is included in the study procedures manual, which is updated as needed.

9.2.2 Investigator's Study Files

Documentation about the investigator and 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 investigational product, biological samples, and the laboratory, the study procedures manual and study logs, eCRFs, records of monitoring activities, and correspondence between sponsor or study monitor and the investigator.

9.2.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site 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 site by the site 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 on computer disc after study closure to be kept in the investigator's study files.

9.2.4 Retention of Study Documents

According to International Council for Harmonisation 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 the another investigator at the institution where the study was conducted.

Audit trails for electronic document 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.

9.3 CONFIDENTIALITY

9.3.1 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).

9.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on eCRFs and other documents retrieved from the site or sent to the study monitor, sponsor, regulatory agencies, central laboratories, or blinded reviewers. Documents that identify the subject (e.g., the signed informed consent form) 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.

9.4 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 informed consent form, the revised informed consent form prepared by the investigator must also be approved by the sponsor, study monitor, and the IRB/IEC before implementation.

Departures from the protocol are allowed only in situations that eliminate an immediate risk to a subject and that are deemed crucial for the safety and well-being of that subject. The investigator or the attending physician also will contact the medical monitor as soon as possible in the case of such a departure. These departures do not require preapproval 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.

9.5 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 International Council for Harmonisation E6, Section 5.18.4.

9.6 GENERAL INFORMATION

The investigator should refer to the Investigator's Brochure, study procedures manual, and any other information provided about this investigational product and details of the procedures to be followed during this study.

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APPENDICES

APPENDIX A

PROTECTION OF HUMAN SUBJECTS
(INTERNATIONAL COUNCIL FOR HARMONISATION E6, SECTION 4.8)

PROTECTION OF HUMAN SUBJECTS

(International Council for Harmonisation E6, Section 4.8)

Informed consent must be obtained from every subject before he or she enters a study. It must be given freely and not under duress. Consent must be documented by the subject or the subject's legally acceptable representative signing an IRB/IEC-approved consent form. When minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent (12 to 16-18 years of age, dependent on region, as specified in ICH E11, Clinical Investigation of Medicinal Products in the Pediatric Population), his or her signature should also be included. Subjects who do not speak English must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given and made available to sponsor and representatives of the appropriate regulatory authority upon request. If, for any reason, subject risk is increased as the study progresses, a revised IRB/IEC-approved consent form must be signed by the subject.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws. Only in the case of a life-threatening incident may an investigational agent be used without prior signed consent. In such an emergency situation, separate certifications must be written by both a physician not participating in the study and the investigator. The certifications, along with the protocol and informed consent form, must be sent to the IRB/IEC within 5 working days. In this situation, the investigator may not administer any subsequent investigational product to that subject until informed consent and IRB/IEC approval are obtained.

BASIC ELEMENTS OF INFORMED CONSENT

Every informed consent form must include explanations of each of the following 22 elements:

- The fact that the trial involves research
- The purpose of the trial
- The trial treatment(s) and the probability for random assignment to each treatment
- The trial procedures to be followed, including all invasive procedures

- The subject's responsibilities

- Those aspects of the trial that are experimental

- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant

- The reasonably expected benefits (When there is no intended clinical benefit to the subject, the subject should be made aware of this.)

- The alternative procedure(s) or course(s) of treatment that may be available to the subject, as well as their important potential benefits and risks

- The compensation or treatment available to the subject in the event of a trial-related injury

- The anticipated prorated payment, if any, to the subject for participating in the trial

- The anticipated expenses, if any, to the subject for participating in the trial

- The fact that the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled

- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of study procedures or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access

- That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws or regulations, will not be made publicly available; and if the results of the trial are published, the subject's identity will remain confidential

- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial

- The person(s) to contact for further information about the trial and the rights of trial subjects, and whom to contact in the event of a trial-related injury

- The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated

- The expected duration of the subject's participation in the trial

- The approximate number of subjects involved in the trial

- The consequences of a subject's decision to withdraw from the research and the procedure for orderly termination of participation by the subject

- That the trial will be included on ClinicalTrials.gov as required by United States law, and, if applicable, the appropriate study database of another regulatory agency (e.g., the Health Canada Clinical Trial Database, EudraCT).

Nothing is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states require further action on the investigator's part concerning subject consent.

APPENDIX B

REQUISITE DOCUMENTS FOR APPROVAL OF STUDY SITE

REQUISITE DOCUMENTS FOR APPROVAL OF STUDY SITE

Investigational product will be provided to the investigators after they have submitted the following documents to the sponsor or study monitor (if applicable):

- Signed statement of investigator (if required by the regulatory agency)
- Institutional review board (IRB) or independent ethics committee (IEC) composition
- Document indicating IRB or IEC approval of the final protocol and amendment(s) if applicable (to include name, address, and chairperson of the IRB or IEC)
- Document indicating IRB or IEC approval of the final and revised informed consent form if applicable (to include name, address, and chairperson of the IRB or IEC)
- Blank copy of the IRB or IEC-approved final and revised informed consent form
- Signed investigator's study agreement and confidentiality disclosure agreement
- Laboratory certification or accreditation and normal ranges for tests that are performed in the laboratory for study assessments
- Curricula vitae for the investigator and subinvestigator(s) listed on the Form FDA 1572 of the study.
- Financial disclosure for the investigator and subinvestigator(s) listed on the Form FDA 1572 of the study.

APPENDIX C

RESPONSIBILITIES AND OBLIGATIONS OF INVESTIGATORS AND SPONSORS

RESPONSIBILITIES AND OBLIGATIONS OF INVESTIGATORS AND SPONSORS

For non–treatment protocols (e.g., separate follow-up protocol, observational protocol), some of the following may not be applicable.

1.0 SPONSOR

The following sections describe the responsibilities and obligation of the sponsor or designee.

1.1 Conduct a site selection visit or study initiation visit to:

1.1.1 Establish the acceptability of the facility and record the visit in a written report (i.e., memorandum or form).

1.1.2 Discuss with the investigator the proposed study and supply him or her with draft electronic case report forms (eCRFs), the Investigator's Brochure, and the draft protocol for his or her review and approval.

1.1.3 Discuss with the investigator the regulatory requirements with respect to informed consent, institutional review board/independent ethics committee (IRB or IEC) approval of the trial, the protocol, protocol amendments, and changes to the informed consent form.

1.1.4 Discuss with the investigator the timing of interim and final reports to the study monitor and his or her obligation to supply the study monitor with copies of all study-related documents (including IRB or IEC approval, IRB or IEC charter or equivalent, membership and qualifications, protocol amendments, informed consent forms, and consent changes), eCRFs, eCRF changes, and all pertinent correspondence to and from the IRB or IEC.

1.2 Conduct periodic on-site visit(s) to:

1.2.1 Ensure adherence to the protocol.

1.2.2 Review eCRFs and source documents for accuracy and completeness of information.

1.2.3 Examine pharmacy records for documentation of quantity and date of receipt of investigational drug, dispensation and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.

1.2.4 Record and report (summarize) observations on the progress of the trial and continued acceptability of the facilities, and prepare an on-site visit report.

1.2.5 Review investigator files for required documents (e.g., protocols; protocol amendments; Investigator's Brochure; study procedures manual; IRB or IEC approval of protocols, amendments, and informed consent form; IRB or IEC charter and membership; and communications to and from the IRB/IEC and the study monitor).

2.0 INVESTIGATOR

2.1 Institutional review board or independent ethics committee

The investigator must assure the study monitor that the IRB or IEC:

2.1.1 Meets International Council for Harmonisation (ICH) guidelines as defined in ICH E6 Section 3, Institutional Review Board/Independent Ethics Committee

2.1.2 Has the authority delegated by the parent institution and found in the IRB or IEC by-laws, operation guidelines, or charter to approve or disapprove clinical studies and protocols, including the informed consent form and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent)

2.1.3 Complies with proper personnel make-up of the board

2.1.4 Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them

2.1.5 Maintains files that contain (a) documentation of its decisions, such as are found in IRB or IEC minutes and correspondence, (b) written guidelines or by-laws governing IRB or IEC functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and information to be supplied to the subject, and (f) correspondence between the IRB or IEC and investigator (e.g., consent changes, protocol amendments)

2.2 Informed consent of human subjects

The investigator must assure the study monitor that the informed consent form for a subject:

2.2.1 Meets ICH guidelines as defined in ICH E6, Section 4.8, Informed Consent of Trial subjects

2.2.2 Has been approved by the IRB or IEC, including (when required) information to be given to the subject about the trial in which he or she is enrolled

2.2.3 Includes the basic elements and any additional elements of informed consent that are appropriate

2.2.4 Has been signed by both the subject (or the subject's legally acceptable representative), the investigator, and a witness, and a copy has been given to the subject

2.2.5 Is provided, if necessary, to the subject in the "short form" informed consent form (presented orally to the subject or the subject's legally acceptable representative, with a witness listening) with written information as an alternative

2.2.6 Allows for assent to be obtained for minor children as required by the IRB or IEC

2.3 Storage and dispensing of product supplies

The investigator (or the investigator's pharmacist) must assure the study monitor that:

2.3.1 Adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.

2.3.2 Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the sponsor.

2.4 Case report forms

The investigator must assure the study monitor that:

2.4.1 The completed eCRF accurately reflects the hospital records for each subject.

2.4.2 The eCRFs and hospital records will be accessible to the study monitor during on-site visits.

2.5 Files and records

The investigator must ensure the quality, integrity, and content of his or her files, which will be subject to audit by the study monitor and the appropriate regulatory authority inspectors. The files must contain, as minimum the following:

- Investigator's Brochure
- Investigator's obligations, including the following:
  1. 21 Code of Federal Regulations (CFR) Part 312.50, General Responsibilities of Sponsors
  2. 21 CFR Part 312.60, General Responsibilities of Investigators
  3. 21 CFR Part 50, Protection of Human Subjects
  4. 21 CFR Part 56, Institutional Review Boards
  - ICH, E6, Guideline for Good Clinical Practice
- IRB or IEC-approved protocol and protocol amendments
- Blank eCRFs (and amendments to eCRF)
- Study procedures manual and amended pages
- Statement of investigator forms (copy of signed Form FDA 1572 and a copy of each revised form if required by the regulatory agency) as well as current curricula vitae and bibliography for each investigator and subinvestigator

- IRB or IEC document, including the following:
  5. IRB or IEC charter membership and qualifications of each member
  6. IRB or IEC letter of approval of protocol and amendments
  7. IRB or IEC letter of approval of informed consent form and amendments
  8. Investigator's annual report to the IRB or IEC
  9. IRB or IEC annual re-approval of protocol
  10. Reports to IRB or IEC of deaths and serious adverse events (SAEs)
  11. Notification to IRB of study completion and investigator's final report
  12. IRB approval of advertisements for subject recruitment (if applicable)
  - All additional correspondence with the IRB/IEC
- IRB/IEC - approved informed consent document (all versions) and information to be supplied to the subject
- Study staff signature log
- Subject accountability records, including the following:
  13. Subject screening log
  14. Medical exceptions log
  15. Site status report
  16. Subject identification code list
  17. Original signed informed consent form
  18. A note stating the location of the eCRFs and data clarification requests
  - Copies of completed eCRF transmittal logs
- Investigation product records, including the following:
  19. Receipt, date and quantity, and batch or lot number
  20. Disposition dates and quantity administered to each subject
  21. Inventory records
  - All correspondence related to the investigational product

- SAE/safety reports
  - Copies of signed SAE reports
  - All SAE correspondence, including MedWatch and Form FDA 3500A

- Biological sample inventory forms and correspondence with the analytical laboratory

- Monitoring activities

22. Monitoring log (should include all visits [i.e., site initiation, periodic, and termination visits])
23. Telephone contact reports
24. Site initiation visit reports

- General Correspondence

25. All correspondence between the study monitor, sponsor, and the site
26. All correspondence between site staff about the protocol

Documents and records must be retained by the investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or for at least 2 years after the formal discontinuation of clinical development of the investigational product.

APPENDIX D

PARTIAL MAYO SCORE QUESTIONNAIRE

HTD1801.PCT003 Study
Partial Mayo Score Questionnaire

Subject #: _____ Subject Initials: _____

Date of visit: _____

Visit Name: Screening ☐ Baseline ☐ Week 6 ☐ Week 12 ☐ Week 18 ☐

Patients will fill out the first two questions, and the physician will fill out the last question.

Patients: please select an option below based on stool frequency in the past 3 days.

1. **Stool Frequency**

☐ Normal number of stools for patient	= 0
☐ 1 to 2 stools per day more than normal	= 1
☐ 3 to 4 stools more than normal	= 2
☐ ≥ 5 stools more than normal	= 3

Patients: please select an option below based on rectal bleeding in the past 3 days.

2. **Rectal Bleeding**

☐ No blood seen	= 0
☐ Streaks of blood with stool less than half of the time	= 1
☐ Obvious blood with stool most of the time	= 2
☐ Blood alone passes	= 3

Physicians: Please select an option below:

3. **Physician's Global Assessment:**

☐ Normal	= 0
☐ Mild disease	= 1
☐ Moderate disease	= 2
☐ Severe disease	= 3

Site staff: To calculate the total score, either enter the responses onto the Partial Mayo Score EDC page of the appropriate visit OR manually calculate the sum using the response values noted above and record total score on the visit worksheet.

Study coordinator or PI initials:_____Date_____