CONFIDENTIAL

CLINICAL PROTOCOL

TITLE OF STUDY:

A Proof-of-Concept and Dose-Ranging Study Investigating the Efficacy and Safety of HTD1801 in Adults with Nonalcoholic Steatohepatitis (NASH) and Type 2 Diabetes Mellitus (T2DM)

Protocol HTD1801.PCT012

Trial Registration: NCT03656744

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Sponsor: **HighTide Biopharma Pty. Ltd.**
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Signatures of Approval of Protocol (Version 3.0)

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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 and Dose-Ranging Study Investigating the Efficacy and Safety of HTD1801 in Adults with Nonalcoholic Steatohepatitis (NASH) and Type 2 Diabetes Mellitus (T2DM)

Investigator(s): Multicenter

Number of sites: Approximately 15

Study periods:
Screening: 28 days
Double-blind Treatment: 18 weeks
Follow-up: 30 days (after last dose of study drug)

Phase of development: 2

Study Design: This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing multiple doses of investigational product (HTD1801) to placebo. Upon confirmation of eligibility, subjects will be randomized in a 1:1:1 ratio to HTD1801 500 mg twice daily (BID), HTD1801 1,000 mg BID, or placebo BID for 18 weeks.

Objectives:

The primary objective of this study is to evaluate the effects of HTD1801 on liver fat content (LFC) in adults with NASH and T2DM.

The secondary objectives of this study are to evaluate:

1. The effects of HTD1801 on hemoglobin A1c (HbA1c) and glucose metabolism;
2. The effects of HTD1801 on lipid profile;
3. The effects of HTD1801 on liver associated enzymes;
4. The effects of HTD1801 on biomarkers of liver inflammation and fibrosis;
5. The effects of HTD1801 on bile acid homeostasis;
6. The safety and tolerability of HTD1801.

Methodology: This is an 18-week randomized, double-blind, parallel-group, proof-of-concept, and dose-ranging study comparing multiple doses of HTD1801 to placebo. Clinic visits for efficacy assessments and safety monitoring will occur at Week 2, then every 4 weeks throughout the Double-Blind Treatment Period. A follow-up safety telephone contact will take place at least 30 days after the last dose of study drug. An interim analysis will be conducted once a minimum of 51 subjects complete the assessment of the primary efficacy endpoint. An independent Data and Safety Monitoring Board will provide additional safety oversight.

Number of subjects (planned): Approximately 117

Inclusion criteria:

1. Male or female between 18 and 75 years of age.
2. Clinical diagnosis of NASH with at least stage F1 fibrosis as evident by:

STUDY SYNOPSIS (continued)

Name of sponsor company: HighTide BioPharma Pty. Ltd.

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- Liver fat content ≥10% as assessed by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) and a corrected T1 (cT1) of ≥830 msec as assessed by multiparametric MRI.

3. Aspartate aminotransferase (AST) ≥20 U/L.
4. Clinically documented diagnosis of T2DM ≥6 months prior to randomization.
5. If on a T2DM medication regimen, specifically thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, or sodium-glucose cotransporter-2 (SGLT-2) inhibitors, must be maintained on a stable dose regimen for ≥90 days prior to randomization.
6. If on vitamin E, must be maintained on a stable dose of ≤400 IU for ≥90 days prior to randomization with no anticipated dose increases during the study.
7. Regimens for other permitted concomitant medications, as described in Section 4.5 of the protocol, must be stable for ≥28 days prior to randomization.
8. Body mass index (BMI) >25 kg/m^2.
9. Females of child-bearing potential (FOCP) 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 at least 90 days after the last dose of study drug. Females who are postmenopausal must have appropriate supporting documentation with a corresponding follicle-stimulating hormone (FSH) test result to support status.
10. Ability to understand and sign a written informed consent form (ICF).

Exclusion criteria:

1. Clinically significant acute or chronic liver disease unrelated to NASH, including but not limited to primary sclerosing cholangitis (PSC), Wilson's disease, alpha-1 antitrypsin (AAT) deficiency (MZ or ZZ phenotype), hepatitis B or C, hereditary hemochromatosis, alcoholic liver disease, and drug-induced liver disease.
2. Clinically or histologically documented cirrhosis.
3. Poorly controlled T2DM (HbA1c ≥9.5%) or Type 1 Diabetes Mellitus.
4. Hepatitis B surface antigen positive.
5. Hepatitis C antibody positive with active infection.
6. Human immunodeficiency virus (HIV)-1 or HIV-2 infection.
7. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
8. Any prior history of hepatic decompensation (encephalopathy, ascites, gastroesophageal varices, hepatorenal syndrome), platelet count <150,000/mm^3, international normalized ratio (INR) ≥1.3 despite vitamin K supplementation, serum albumin <3.2 g/dL, or a prior or planned liver transplantation.
9. History of alcohol or substance abuse or dependence.
10. Hepatic steatosis that, in the opinion of the Investigator, is primarily related to alcohol consumption.
11. Inability to undergo MRI for any reason.

STUDY SYNOPSIS (continued)

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Note: Mild sedative use (if not prohibited as described in Section 4.6 of the protocol) for MRI procedures is permitted.

12. Laboratory parameters within any of the following ranges:
    - AST >5 × ULN.
    - Alanine aminotransferase (ALT) ≥5 × ULN.
    - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
    - Hemoglobin <11 g/dL for males or females.
    - Direct bilirubin <LLN or >ULN.
    - Total bilirubin <LLN or >ULN.

      Note: Total bilirubin >ULN due to Gilbert's syndrome is acceptable provided that direct bilirubin, reticulocyte count, and hemoglobin are within the laboratory defined normal ranges.
    - Thyroid-stimulating hormone (TSH) <LLN or >1.5 × ULN.

      Note: Subjects on a medication for a thyroid abnormality may enroll provided that they have been maintained on a stable dose for ≥90 days prior to randomization.
13. Current use of oral prednisone/prednisolone (or prednisone/prednisolone equivalent) >10 mg/day.
14. History of myocardial infarction, congestive heart failure, uncontrolled cardiac arrhythmia, unstable angina, coronary bypass surgery, or percutaneous coronary intervention ≤12 months prior to Screening.
15. History of malignancy ≤2 years prior to Screening or ongoing malignancy other than basal cell carcinoma, or resected noninvasive cutaneous squamous cell carcinoma.
16. Active, serious infections that require parenteral antibiotic or antifungal therapy ≤30 days prior to Screening.
17. Major surgical procedure ≤30 days prior to Screening or prior organ transplantation.
18. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents, and immune-modulating agents.
19. Current use of prohibited medications as described in Section 4.6 of the protocol.
20. Females who are pregnant or breastfeeding.
21. Allergy to the study drug or its components.
22. Use of any unapproved treatment for NASH, including but not limited to ursodeoxycholic acid (UDCA) and berberine containing agents, ≤30 days prior to Screening.
23. Participation in other clinical trials of investigational drugs for NASH ≤6 months prior to Screening.
24. Received any investigational drugs for any other condition ≤30 days or 5 half-lives (whichever is longer) prior to Screening.
25. Any other clinically significant laboratory parameters, disorders, or prior or current therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study, unable to comply with the dosing and protocol requirements, or could confound the study outcomes.

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)

Test product, dose, and mode of administration:

- HTD1801: 250 mg tablets administered as 500 mg BID or 1,000 mg BID with food.
- Placebo: HTD1801-matching tablets administered BID with food.

Reference therapy, dose and mode of administration:

Not applicable.

Duration of treatment: 18 weeks

Criteria for Evaluation:

Efficacy Evaluation

Primary Efficacy Endpoint:

The primary endpoint for this study is the absolute change in LFC as measured by MRI-PDFF from Baseline to Week 18.

Secondary Efficacy Endpoints:

1. Changes in fasting glucose and HbA1c from Baseline to Week 18.
2. Proportion of subjects who achieve ≥30% relative reduction in LFC as measured by MRI-PDFF from Baseline to Week 18.
3. Relative change in LFC as measured by MRI-PDFF from Baseline to Week 18.
4. Proportion of subjects who normalize LFC to <5% as measured by MRI-PDFF at Week 18.
5. Proportion of subjects who achieve ≥5% absolute reduction in LFC as measured by MRI-PDFF from Baseline to Week 18.
6. Change in homeostasis model assessment-estimated insulin resistance (HOMA-IR) from Baseline to Week 18.
7. Change in low-density lipoprotein cholesterol (LDL-c) from Baseline to Week 18.
8. Change in serum triglycerides from Baseline to Week 18.
9. Change in high-density lipoprotein cholesterol (HDL-c) from Baseline to Week 18.
10. Changes in AST and ALT from Baseline to Week 18.
11. Proportion of subjects with elevated ALT at Baseline who normalize ALT at Week 18.
12. Change in Pro-C3 from Baseline to Week 18 for subjects with elevated Pro-C3 at Baseline.
13. Change in the enhanced liver fibrosis (ELF) score and each component of ELF (tissue inhibitor of metalloproteinases 1 [TIMP-1], N-terminal pro-peptide of type III collagen [PIIINP], and hyaluronic acid [HA]) from Baseline to Week 18.
14. Changes in total bile acids, 7α-hydroxy-4-cholesten-3-one (C4), and fibroblast growth factor 19 (FGF19) from Baseline to Week 18.

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)

Analysis of Primary Endpoint:

The primary endpoint is absolute change from Baseline to Week 18 in LFC, or absolute change from Baseline to the Early Termination (ET) visit for subjects who terminate the study prematurely. Absolute change from Baseline in LFC will be assessed by analysis of covariance that includes the effects of treatment group, Baseline LFC, and Baseline ALT. Comparison of each active treatment group to placebo will be tested at the 5% level of significance without adjustment for multiple tests. Secondarily, comparison of the 2 active treatment groups with each other will be tested at the 5% level.

Analysis of Secondary Endpoints:

Relative (percent) change from Baseline in LFC will be analyzed by the same model described for the primary endpoint. Normalization of LFC will be analyzed by logistic regression that includes the effects of treatment group, Baseline LFC, and Baseline ALT.

All additional secondary endpoints are continuous and each will be assessed by analysis of covariance that includes treatment group and the Baseline value of the analysis variable. All secondary analyses (except LFC) will have missing Week 18 values imputed using a multiple imputation procedure for all subjects with an available measurement prior to Week 18.

Safety Evaluation

Safety Endpoints:

Adverse events and changes in physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory values will be used to evaluate safety and tolerability. Adverse event incidence will be assessed during the Double-Blind Treatment Period. Adverse event type, relationship, severity, onset, and duration will be presented by treatment group within the Double-Blind Treatment Period.

Safety Analysis:

Changes in physical examination, vital signs, ECG, and clinical laboratory values will be presented using summary statistics. Numbers and percentages of the first occurrence for each adverse event will be presented.

Sample Size:

An absolute change in LFC of 5% as measured by MRI-PDFF has been reported to be the minimal clinically relevant difference between active treatment and placebo that correlates with histological improvement in NASH (Loomba et al., 2015, Patel et al., 2015). Furthermore, Harrison and colleagues reported a pooled standard deviation of 6.3% for changes from Baseline in LFC (Harrison et al., 2018). Based on this standard deviation, 35 subjects in each treatment group will provide 90% power to show a difference of 5 percentage points between any 2 treatment groups at the 5% level of significance. To allow for a dropout rate of 10%, 39 subjects will be randomized to each of the 3 treatment groups. An interim analysis will be conducted after a minimum of 51 subjects complete the assessment of the primary efficacy endpoint to assess sample size assumptions and futility through conditional power; the study will not be stopped for efficacy.

Figure 1. Study Design

Screening	Double-Blind Treatment						Follow-up
	Baseline	WK 2	WK 6	WK 10	WK 14	WK 18	

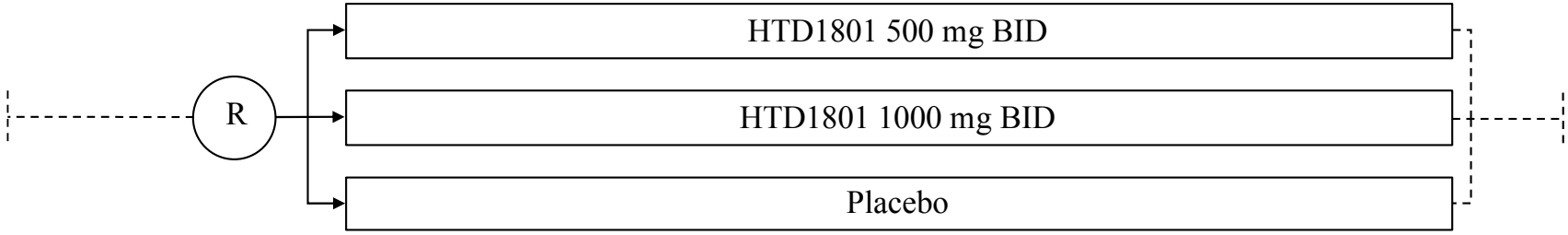

Table 1. Schedule of Time and Events

	Protocol Section(s)	SCR	Double-Blind Treatment						ET	Follow-up
			Baseline	WK 2	WK 6	WK 10	WK 14	WK 18		
Visit Day	-	-28 to -1	0	14	42	70	98	126	-	+30d
Procedure / Window		-	-	±3d	±3d	±3d	±3d	±3d		+7d
Administrative Procedures										
Clinic visit	5.1	X	X	X	X	X	X	X	X	
Informed consent	10.1	X								
Eligibility criteria	3.3.1, 3.3.2	X	X[a]							
Demographics	6.1.1	X								
Medical history	6.1.1	X	X[a]							
Randomization	6.1.2		X							
Dispense study drug	6.1.2		X	X	X	X	X			
Return study drug	6.1.2			X	X	X	X	X	X	
Study discharge	5.1.4, 5.1.5							X	X	
Telephone contact	5.1.6									X
Clinical Assessments										
Comprehensive physical examination	6.3.1	X						X	X	
Targeted physical examination[b]	6.3.1		X[a]		X		X			
Vital signs	6.3.2	X	X[a]		X		X	X	X	
Weight	6.3.2	X	X[a]	X	X	X	X	X	X	
Height	6.3.2	X								
ECG	6.3.3	X	X[a]		X		X	X	X	
Laboratory Assessments										
Serum chemistry panel[c]	6.2.2, 6.3.4	X	X	X	X	X	X	X	X	
Lipid panel[c]	6.2.2, 6.3.4	X	X			X		X	X	
Hematology with differential[c]	6.3.4	X	X			X		X	X	
Coagulation panel[c]	6.3.4	X	X			X		X	X	

	Protocol Section(s)	SCR	Double-Blind Treatment						ET	Follow-up
			Baseline	WK 2	WK 6	WK 10	WK 14	WK 18		
Visit Day	-	**-28 to -1**	**0**	**14**	**42**	**70**	**98**	**126**	-	**+30d**
Procedure / Window		**-**	**-**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**		**+7d**
HbA1c	6.2.2	X[d]				X		X	X	
HOMA-IR	6.2.2		X					X	X	
HIV and Hepatitis B/C	6.3.4	X								
G6PD	6.3.4	X								
Pregnancy test[e]	6.3.4	X	X[a,e]					X	X	
FSH test[e]	6.3.4	X								
Urine drug test	6.3.4	X								
Imaging and Biomarker Assessments										
MRI-PDFF	6.2.1	X[d]						X	X	
Corrected T1 and T2*	6.2.1	X[d]								
Pro-C3	6.2.2		X					X	X	
ELF test	6.2.2		X					X	X	
Bile acid panel[c]	6.2.2		X			X		X	X	
Safety Assessments										
Adverse event monitoring	6.3.5, 7.0	X	X[a]	X	X	X	X	X	X	X
Prior and concomitant medications	4.5, 4.6, 6.3.6	X	X[a]	X	X	X	X	X	X	X

[a] Continued study eligibility confirmed based on updated medical history, targeted physical examination, vital signs, weight, ECG, negative urine pregnancy test (for FOCP), updated prior and concomitant medications, and any adverse events that have occurred since signing informed consent.

[b] Targeted physical examination of body systems or organs performed on symptom-driven basis (e.g., adverse events or other findings).

[c] See Table 2 for analytes tested as part of the serum chemistry, lipid, hematology, and coagulation panels. The serum chemistry panel performed at the Week 2, Week 6, and Week 14 visits only includes testing of alkaline phosphatase (ALP), ALT, AST, gamma-glutamyl transferase (GGT), total bilirubin, direct bilirubin, and fasting glucose. The Week 10 and Week 18 (or ET) bile acid panel applies only to subjects who have had the Baseline bile acid panel performed.

[d] Assessments performed during Screening to confirm study eligibility; results applied as Baseline values.

[e] Pregnancy test required for FOCP only; serum pregnancy test performed at Screening and Week 18 (or ET); urine and confirmatory serum pregnancy tests performed at Baseline. FSH test required for postmenopausal females only.

ET = Early Termination; SCR = Screening

Table 2. Laboratory Analytes

Serum Chemistry	Hematology	Lipids	Coagulation
Comprehensive metabolic panel: • Albumin • ALP • ALT • AST • Bicarbonate • Bilirubin, total • Bilirubin, direct • Blood urea nitrogen (BUN) • Calcium • Chloride • Creatinine • Creatine kinase • GGT • Glucose, fasting • Lactate dehydrogenase • Magnesium • Phosphorus • Potassium • Sodium • Total protein • Uric acid Endocrinology: • Insulin, fasting • TSH	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count • Reticulocyte count White blood cell count differential, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Total cholesterol LDL-c HDL-c Triglycerides	Activated partial thromboplastin time (aPTT) Prothrombin time (PT) INR **Other** HbA1c HOMA-IR HIV and Hepatitis B/C G6PD Serum and urine pregnancy tests FSH test Urine drug test Pro-C3 ELF Bile acid panel, including: • Bile acids, total • C4 • FGF19

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AAT	alpha-1 antitrypsin
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BBR	berberine
BBR·Cl	berberine chloride
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C4	7α-hydroxy-4-cholesten-3-one
cT1	corrected T1
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DILI	drug induced liver injury
DPP-4	dipeptidyl peptidase-4
DSHEA	Dietary Supplement Health and Education Act
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
EDC	electronic data capture
ELF	enhanced liver fibrosis
ET	early termination
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
FOCP	females of child-bearing potential
FSH	follicle-stimulating hormone
FXR	farnesoid X receptor
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
HA	hyaluronic acid
HbA1c	hemoglobin A1c
HDL-c	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homoeostasis model assessment-estimated insulin resistance
ICF	informed consent form

ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
LDL-c	low-density lipoprotein cholesterol
LFC	liver fat content
LMSD	*Liver*MultiScan *Discover*™
MRI-PDFF	magnetic resonance imaging-estimated proton density fat fraction
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
P-gp	P-glycoprotein
PBC	primary biliary cirrhosis
PET/AL/PE	polyethylene terephthalate/aluminum foil/polyethylene
PIIINP	N-terminal pro-peptide of type III collagen
PK	pharmacokinetic
POC	proof-of-concept
PSC	primary sclerosing cholangitis
PT	prothrombin time
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGLT-2	sodium-glucose cotransporter-2
SPM	Study Procedures Manual
T2DM	Type 2 Diabetes Mellitus
TB	total bilirubin
TC	total cholesterol
TIMP-1	tissue inhibitor of metalloproteinases-1
TSH	thyroid-stimulating hormone
UDCA	ursodeoxycholic acid
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States

1.0 INTRODUCTION

HTD1801 is a novel salt formed between berberine (BBR) and ursodeoxycholic acid (UDCA) with a stoichiometry of 1:1. HTD1801 is currently being developed as an oral treatment for nonalcoholic steatohepatitis (NASH). HTD1801 is expected to dissociate into BBR salt and UDCA after oral administration, which suggests that the efficacy and safety profiles of HTD1801 can be predicted by those of the individual components (see Section 1.1.1.1).

Berberine and UDCA have displayed wide-ranging biologic activity relative to liver dysfunction in nonclinical and clinical settings, including immunomodulatory, anti-inflammatory, anti-fibrotic, anti-microbial, and hepatoprotective effects. Furthermore, their effects on serum lipid, hepatic lipid, and/or glucose metabolism, all of which are implicated in the pathogenesis of NASH, have been well studied and reported in the literature.

Given the reported hepatotherapeutic mechanisms of BBR and UDCA, the pharmacologic profile of HTD1801 (see Section 1.1.1.2) may offer patients with NASH a safe and effective therapy. HighTide Biopharma Pty. Ltd. (HighTide) is conducting this proof-of-concept (POC) study to evaluate HTD1801 in adults with NASH and Type 2 Diabetes Mellitus (T2DM) by assessing changes in liver fat content (LFC) over 18 weeks.

1.1 BACKGROUND

1.1.1 Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis is a progressive form of nonalcoholic fatty liver disease (NAFLD) characterized by the presence of hepatic steatosis and inflammation with hepatocyte injury (i.e., ballooning) with or without fibrosis. While the prevalence of NAFLD in the general population is estimated at 20-30%, NASH has been reported to affect approximately 5% of the general population. It is generally agreed that patients with NASH can exhibit histological progression to cirrhotic-stage disease. Furthermore, several studies have reported that the most common cause of death in patients with NAFLD/NASH is cardiovascular disease, while patients specifically with NASH have an increased liver-related mortality rate (Chalasani et al., 2012, NICE

2016). The most common comorbidities associated with NASH are reported to include obesity, T2DM, insulin resistance, hypertension, and dyslipidemia (Rinella 2015).

It is hypothesized that different pathogenic factors lead to "multiple hits" during the disease progression from hepatic steatosis to the hepatic inflammatory and hepatocellular damage components that define NASH (Adams and Angulo 2006, Weiss et al., 2014). Accumulation of hepatic fat linked to insulin resistance is considered the "first hit." Hyperinsulinemia in the context of insulin resistance leads to an increased release of free fatty acids from adipocytes and myocytes, which are then absorbed by and accumulate in the liver resulting in steatosis. Insulin resistance also promotes *de novo* triglyceride synthesis within the liver and inhibits fatty acid oxidation thereby promoting triglyceride accumulation (Adams and Angulo 2006). Additional oxidative injury has been proposed as a "second hit," which manifests the necroinflammatory component of steatohepatitis. Factors associated with obesity and metabolic syndrome, such as increased circulating free fatty acids, excess iron, and intestinal bacterial overgrowth, increase levels of reactive oxygen species and produce cytotoxic aldehydes, which further contribute to oxidative stress and promote hepatocyte injury, inflammation, and apoptosis (Basaranoglu et al., 2013). As hepatocyte injury becomes repetitive and repair dysregulated, the liver's normal wound-healing process stalls during tissue reconstruction and progression to fibrosis and cirrhosis ensues (Diehl and Day 2017).

Despite the investigation of multiple therapies, there are no approved drugs for the treatment of NAFLD, or more specifically, NASH. Currently, weight loss is the only therapy with reasonable evidence suggesting that it is safe, beneficial, and may result in improved histologic features of NASH. Many patients, however, do not achieve or cannot maintain goals of lifestyle modification for a long-term period (Vilar-Gomez et al., 2015). Novel pharmacologic therapies that comprehensively ameliorate the pathological spectrum of NASH are therefore needed.

1.1.1.1 Berberine and Ursodeoxycholic Acid

Berberine is an isoquinoline alkaloid found in many different plants, with a long history of use in traditional Chinese medicine (Caliceti et al., 2016, Kumar et al., 2015). Berberine chloride (BBR·Cl) is an approved antiseptic drug in China, Japan, and Taiwan. In the United States (US) 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 US (Council for Responsible Nutrition 1998). The reported multi-spectrum activity of BBR, including effects on glucose and lipid metabolism, hepatic steatosis, oxidative stress, inflammation, and fibrosis suggests that BBR has the potential to treat NAFLD/NASH. Furthermore, clinical studies of BBR for the treatment of T2DM, hyperlipidemia, hypertension, and NAFLD have yielded favorable results (Cicero and Ertek 2009, Lan et al., 2015).

Ursodeoxycholic acid is a secondary bile acid produced by intestinal bacteria as a metabolic by-product, which is approved by the US Food and Drug Administration (FDA) for the non-surgical treatment of cholesterol gallstone dissolution (Actigall®, NDA 019594) and the treatment of primary biliary cirrhosis (PBC) (URSO 250® and URSO Forte®, NDA 020675). Similar to BBR, UDCA activity is reported to include anti-oxidative stress, anti-inflammatory, anti-apoptotic, and anti-fibrotic effects, as well as improvement in liver injury caused by microbial dysbiosis. In the clinical setting, favorable results were reported for UDCA combination therapy compared to UDCA monotherapy in the treatment of NASH (Xiang et al., 2013).

Based on the pharmacological properties and clinical evaluations of BBR and UDCA relative to NASH and conditions that are most commonly attributed to its development, BBR and UDCA may present as good "partners" for effectively treating this advanced liver disease. More information about the activity, safety, and efficacy of BBR and UDCA can be found in the HTD1801 Investigator's Brochure.

1.1.1.2 HTD1801

HTD1801 is expected to demonstrate a multi-functional pharmacologic profile reflecting the individual actions of its active components, BBR and UDCA. These agents target multiple aberrant pathways that may contribute to the pathogenesis of NASH. The beneficial effects of HTD1801 in patients with NASH are expected to include, but may not be limited to:

- Improved insulin resistance and regulation of lipid and glucose metabolism;
- Reduction of fat deposition in the liver;
- Restoration of the intestinal barrier function;

- Anti-inflammatory, anti-oxidative, and anti-apoptotic effects;
- Anti-fibrotic effects.

Given the unique pharmacologic profiles of BBR and UDCA, both additive and synergistic effects are expected to occur when the 2 products are administered together as HTD1801. More information about the activity, safety, and efficacy of HTD1801 can be found in the HTD1801 Investigator's Brochure.

1.1.2 Nonclinical Studies

The pharmacology of HTD1801 was evaluated *in vivo* in rodent and primate models of hyperlipidemia/NAFLD:

- HTD1801 was evaluated in a pilot study of high-fat diet-induced Golden Syrian hamsters. After 8 weeks, hamsters administered HTD1801 100 mg/kg or a physical mixture of BBR·Cl and UDCA 100 mg/kg (molar ratio of 1:1) had decreased serum levels of total cholesterol (TC), triglycerides, and malondialdehyde compared to those of a model (untreated) control group; however, the effects were enhanced with HTD1801 compared to the physical mixture of BBR·Cl and UDCA. Hamsters treated with the physical mixture of BBR·Cl and UDCA also exhibited greater decreases in body weight and more serious adverse effects than the group treated with HTD1801.
- HTD1801 was further evaluated in a high-fat diet-induced Golden Syrian hamster model of hyperlipidemia/NAFLD. At doses of 50 mg/kg or 200 mg/kg administered intragastrically for 7 weeks, HTD1801 significantly reduced serum levels of TC, triglyceride, and low-density lipoprotein cholesterol (LDL-c), the ratio of TC/high-density lipoprotein cholesterol (HDL-c), and the atherosclerotic index value, as well as the risk of atherosclerosis, in a dose-dependent manner. Hepatic lipidosis and body lipidosis also were significantly reduced, while hepatic inflammation was ameliorated.
- HTD1801 was evaluated in male Rhesus monkeys with naturally-occurring NAFLD. Study results indicated a dose-dependent reduction of liver steatosis. At 30 mg/kg (equivalent to a clinical proposed dose of 1,050 mg/70 kg person/day), HTD1801 significantly reduced liver steatosis, while at 15 mg/kg (equivalent to a clinical proposed dose of 525 mg/70 kg person/day), a decreasing trend in

steatosis was observed after 69 days of administration. Significant lowering of LDL-c, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels was noted, while a treatment-related decreasing trend was observed for TC, apolipoprotein B, and blood glucose levels.

The nonclinical toxicity profiles of both BBR and UDCA have been extensively documented. A full International Conference on Harmonisation (ICH) M3 battery of nonclinical studies of UDCA was submitted in support of NDA 020675. The toxicity profile of BBR was assessed in a battery of 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, and reproductive and developmental toxicity studies in mice and rats (National Toxicology Program 2002, 2003c, a, b, 2010).

The pharmacokinetic (PK) and toxicity profiles of HTD1801 have been evaluated in both rats and dogs. Toxicology studies of up to 2 weeks in rats (non-GLP) and up to 13 weeks in dogs (GLP) have been conducted. Combined administration of BBR and UDCA as HTD1801 yielded PK and toxicity profiles similar to those of the individual components UDCA and BBR. In addition, a 13-week GLP dog study provided data to qualify the toxicity profile of BBR in non-rodents and the safety of the combination of BBR and UDCA when administered as HTD1801.

Available nonclinical study data for HTD1801, together with cumulative nonclinical study data and clinical experience for BBR and UDCA individually, support the safety and tolerability of HTD1801 for this POC study. More information about the nonclinical evaluation of HTD1801 can be found in the HTD1801 Investigator's Brochure.

1.2 STUDY RATIONALE

1.2.1 Rationale for Study Design

This 18-week randomized, double-blind, parallel-group, POC, dose-ranging study will compare multiple doses of HTD1801 to placebo. A randomized, double-blind design will enhance study rigor and quality relative to assessment of the pre-specified endpoints (see Section 3.4). In the absence of approved or recognized therapeutics for NASH, a placebo control group will be utilized, as has been reported for several prior

randomized, placebo-controlled assessments of various pharmacologic agents (Loomba et al., 2008).

Since accumulation of hepatic fat is considered the "first hit" in the pathogenesis of NASH (Adams and Angulo 2006), change in LFC by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) is an appropriate primary endpoint and is consistent with that used in recent Phase 2 POC studies in NASH (Harrison et al., 2018, Madrigal Pharmaceuticals 2018).

1.2.2 Rationale for Dose and Duration

Ursodeoxycholic acid is approved by the US FDA at a dose of 13-15 mg/kg/day (URSO 250® and URSO FORTE®), or approximately 1 g/day for a 70 kg individual. Berberine is widely used in dietary supplements in the US at a recommended dose of 17-33 mg/kg/day, or approximately 1-2 g/day for a 70 kg individual. Furthermore, New Tantose A®, an over-the-counter combination including BBR (adult dose of 0.300 g/day) and UDCA (0.030 g/day), has been approved in Japan for acute diarrheal illness (New Tantose A®), while the therapeutic dosage in most of BBR's clinical experience is around 0.4-2.7 g/day orally for exposures up to 181 days (Cicero and Ertek 2009, Lan et al., 2015). As shown in Table 3, the UDCA and BBR content of HTD1801 are comparable to doses associated with clinical safety.

Table 3. Comparison of HTD1801 Clinical Dose with FDA Approved UDCA Dose and Clinical BBR Dose

Compound	FDA Approved Clinical Dose (UDCA) / Dose Used in Clinical Experience (BBR)	HTD1801 Clinical Dose (29 mg/kg/day; 2,000 mg/day)[a,d]
UDCA[a]	13-15 mg/kg/day (910-1,050 mg/day)[b]	15 mg/kg/day (1,078 mg/day)
BBR[a]	6-38 mg/kg/day (400-2,700 mg/day)[c]	15 mg/kg/day (1,022 mg/day)

[a] mg/kg doses calculated assuming a 70 kg adult.

[b] Safety at doses up to 25 mg/kg/day is supported by the published literature for PBC patients (Angulo et al., 1999).

[c] Therapeutic dosage in most of BBR's clinical experience (Cicero and Ertek 2009, Lan et al., 2015).

[d] HTD1801 dose of 2,000 mg/day is equivalent to 1,022 mg/day BBR and 1,078 mg/day UDCA.

Furthermore, data from a first-in-human, single ascending dose study of HTD1801 in healthy subjects (Protocol HTD1801.PCT002) demonstrated dose proportionality for

UDCA and BBR exposure parameters at orally administered HTD1801 doses of 0.5-4.0 g/day. Single doses of HTD1801 were also safe and well tolerated.

Lastly, recent Phase 2 POC studies in NASH (Harrison et al., 2018, Madrigal Pharmaceuticals 2018) show clinically meaningful absolute and relative reductions in LFC assessed by MRI-PDFF over 12-week treatment periods. An 18-week HTD1801 treatment period is therefore adequate to assess the study's primary endpoint and to maximize collection of exposure and safety related data.

2.0 OBJECTIVES

The primary objective of this study is to evaluate the effects of HTD1801 on LFC in adults with NASH and T2DM.

The secondary objectives of this study are to evaluate:

1. The effects of HTD1801 on hemoglobin A1c (HbA1c) and glucose metabolism;
2. The effects of HTD1801 on lipid profile;
3. The effects of HTD1801 on liver-associated enzymes;
4. The effects of HTD1801 on biomarkers of liver inflammation and fibrosis;
5. The effects of HTD1801 on bile acid homeostasis;
6. The safety and tolerability of HTD1801.

3.0 STUDY DESIGN

3.1 BASIC DESIGN CHARACTERISTICS

This multicenter, randomized, double-blind, parallel-group, POC and dose-ranging study will compare multiple doses of HTD1801 to placebo. Upon confirmation of eligibility, subjects will be randomized in a 1:1:1 ratio to receive 1 of 2 doses of HTD1801 or placebo for 18 weeks.

Subjects will receive 500 mg HTD1801, 1,000 mg HTD1801, or placebo (collectively, the study drug or study drugs), administered twice daily (BID) during the 18-week Double-Blind Treatment Period. Clinic visits for efficacy assessments and safety monitoring will occur at Week 2, then every 4 weeks throughout the Double-Blind Treatment Period. A follow-up safety telephone contact for an assessment of adverse events (AEs) and concomitant medications will take place at least 30 days after the last dose of study drug. An interim analysis will be conducted after a minimum of 51 subjects complete the assessment of the primary efficacy endpoint to assess sample size assumptions and futility through conditional power; the study will not be stopped for efficacy. An independent Data and Safety Monitoring Board (DSMB) will provide additional safety oversight.

3.2 DURATION OF SUBJECT PARTICIPATION AND STUDY

Once the informed consent form (ICF) is signed, Screening assessments (see Section 5.1.1) may be performed over a 28-day period prior to randomization at the Baseline visit. Subjects will then be randomized to receive their assigned study drug during the 18-week Double-Blind Treatment Period (see Section 5.1.3). If a subject completes the Double-Blind Treatment Period or discontinues his/her assigned study drug early, the subject will complete follow-up assessments (see Section 5.1.5) at least 30 days after the last dose of study drug. Overall subject participation, from Screening through the follow-up assessments, may last for up to approximately 6 months.

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have discontinued taking their assigned study drug (i.e., either at the end of the Double-Blind Treatment Period or earlier) and have completed the follow-up assessments.

3.3 STUDY POPULATION

Approximately 117 patients with NASH and T2DM will be enrolled as subjects from approximately 15 investigational sites in the US. Eligibility will be established by the Investigator on the basis of the inclusion and exclusion criteria.

3.3.1 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. Clinical diagnosis of NASH with at least stage F1 fibrosis as evident by:
    - Liver fat content ≥10% as assessed by MRI-PDFF and a corrected T1 (cT1) of ≥830 msec as assessed by multiparametric MRI.
3. Aspartate aminotransferase ≥20 U/L.
4. Clinically documented diagnosis of T2DM ≥6 months prior to randomization.
5. If on a T2DM medication regimen, specifically thiazolidinediones, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, or sodium-glucose cotransporter-2 (SGLT-2) inhibitors, must be maintained on a stable dose regimen for ≥90 days prior to randomization.
6. If on vitamin E, must be maintained on a stable dose of ≤400 IU for ≥90 days prior to randomization with no anticipated dose increases during the study.
7. Regimens for other permitted concomitant medications, as described in Section 4.5 of the protocol, must be stable for ≥28 days prior to randomization.
8. Body mass index (BMI) >25 kg/m^2.
9. Females of child-bearing potential (FOCP) 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 at least 90 days after the last

dose of study drug. Females who are postmenopausal must have appropriate supporting documentation with a corresponding follicle-stimulating hormone (FSH) test result to support status.

10. Ability to understand and sign a written ICF.

3.3.2 Exclusion Criteria

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

1. Clinically significant acute or chronic liver disease unrelated to NASH, including but not limited to primary sclerosing cholangitis (PSC), Wilson's disease, alpha-1 antitrypsin (AAT) deficiency (MZ or ZZ phenotype), hepatitis B or C, hereditary hemochromatosis, alcoholic liver disease, and drug induced liver disease.
2. Clinically or histologically documented cirrhosis.
3. Poorly controlled T2DM (HbA1c ≥9.5%) or Type 1 Diabetes Mellitus.
4. Hepatitis B surface antigen positive.
5. Hepatitis C antibody positive with active infection.
6. Human immunodeficiency virus (HIV)-1 or HIV-2 infection.
7. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
8. Any prior history of hepatic decompensation (encephalopathy, ascites, gastroesophageal varices, hepatorenal syndrome), platelet count <150,000/mm^3, international normalized ratio (INR) ≥1.3 despite vitamin K supplementation, serum albumin <3.2 g/dL, or a prior or planned liver transplantation.
9. History of alcohol or substance abuse or dependence.
10. Hepatic steatosis that, in the opinion of the Investigator, is primarily related to alcohol consumption.
11. Inability to undergo MRI for any reason.

Note: Mild sedative use (if not prohibited as described in Section 4.6 of the protocol) for MRI procedures is permitted.

12. Laboratory parameters within any of the following ranges:

    - AST >5 × ULN.
    - ALT ≥5 × ULN.
    - Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.
    - Hemoglobin <11 g/dL for males or females.
    - Direct bilirubin <LLN or >ULN.
    - Total bilirubin <LLN or >ULN.

      Note: Total bilirubin >ULN due to Gilbert's syndrome is acceptable provided that direct bilirubin, reticulocyte count, and hemoglobin are within the laboratory defined normal ranges.

    - Thyroid-stimulating hormone (TSH) <LLN or >1.5 × ULN.

      Note: Subjects on a medication for a thyroid abnormality may enroll provided that they have been maintained on a stable dose for ≥ 90 days prior to randomization.

13. Current use of oral prednisone/prednisolone (or prednisone/prednisolone equivalent) >10 mg/day.

14. History of myocardial infarction, congestive heart failure, uncontrolled cardiac arrhythmia, unstable angina, coronary bypass surgery, or percutaneous coronary intervention ≤12 months prior to Screening.

15. History of malignancy ≤2 years prior to Screening or ongoing malignancy other than basal cell carcinoma, or resected noninvasive cutaneous squamous cell carcinoma.

16. Active, serious infections that require parenteral antibiotic or antifungal therapy ≤30 days prior to Screening.

17. Major surgical procedure ≤30 days prior to Screening or prior organ transplantation.

18. Current or anticipated treatment with radiation therapy, cytotoxic chemotherapeutic agents, and immune-modulating agents.

19. Current use of prohibited medications as described in Section 4.6 of the protocol.

20. Females who are pregnant or breastfeeding.

21. Allergy to the study drug or its components.

22. Use of any unapproved treatment for NASH, including but not limited to UDCA and berberine containing agents, ≤30 days prior to Screening.

23. Participation in other clinical trials of investigational drugs for NASH ≤6 months prior to Screening.

24. Received any investigational drugs for any other condition ≤30 days or 5 half-lives (whichever is longer) prior to Screening.

25. Any other clinically significant laboratory parameters, disorders, or prior or current therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study, unable to comply with the dosing and protocol requirements, or could confound the study outcomes.

3.4 ENDPOINTS

3.4.1 Efficacy

3.4.1.1 Primary Endpoint

The primary endpoint for this study is the absolute change in LFC as measured by MRI-PDFF from Baseline to Week 18. Analysis of the primary endpoint is described in Section 9.2.3.1.

3.4.1.2 Secondary Endpoints

The secondary endpoints of this study include the following:

1. Changes in fasting glucose and HbA1c from Baseline to Week 18.

2. Proportion of subjects who achieve ≥30% relative reduction in LFC as measured by MRI-PDFF from Baseline to Week 18.

3. Relative change in LFC as measured by MRI-PDFF from Baseline to Week 18.

4. Proportion of subjects who normalize LFC to <5% as measured by MRI-PDFF at Week 18.

5. Proportion of subjects who achieve ≥5% absolute reduction in LFC as measured by MRI-PDFF from Baseline to Week 18.

6. Change in homeostasis model assessment-estimated insulin resistance (HOMA-IR) from Baseline to Week 18.

7. Change in LDL-c from Baseline to Week 18.

8. Change in serum triglycerides from Baseline to Week 18.

9. Change in HDL-c from Baseline to Week 18.

10. Changes in AST and ALT from Baseline to Week 18.

11. Proportion of subjects with elevated ALT at Baseline who normalize ALT at Week 18.

12. Change in Pro-C3 from Baseline to Week 18 for subjects with elevated Pro-C3 at Baseline.

13. Change in the enhanced liver fibrosis (ELF) score and each component of ELF (tissue inhibitor of metalloproteinases 1 [TIMP-1], N-terminal pro-peptide of type III collagen [PIIINP], and hyaluronic acid [HA]) from Baseline to Week 18.

14. Changes in total bile acids, 7α-hydroxy-4-cholesten-3-one (C4), and fibroblast growth factor 19 (FGF19) from Baseline to Week 18.

Analysis of the secondary endpoints is described in Section 9.2.3.2.

3.4.2 Safety

Adverse events and changes in physical examination, vital signs, electrocardiogram (ECG), and clinical laboratory values will be used to evaluate safety and tolerability. Adverse event incidence will be determined during the Double-Blind Treatment Period. Adverse event type, relationship, severity, onset, and duration will be presented by treatment group within the Double-Blind Treatment Period.

3.5 SUBJECT NUMBERING, RANDOMIZATION, AND BLINDING

After signing the ICF, subjects will be assigned a unique subject ID number, which is a combination of the investigational site ID number and a sequential subject number. The subject ID number will be maintained throughout the course of the study and will be the primary number used to manage subject-related operations and documentation. The process for subjects who fail Screening but then repeat the Screening process due to a change in their eligibility status (see Section 5.1.1) will be described in the Study Procedures Manual (SPM) or other applicable instructions.

Upon confirmation of subject eligibility at the Baseline visit (see Section 5.1.2), investigational site staff will login to the designated automated system to randomize the subject. Subjects will be randomized in equal numbers to 1 of 3 treatment groups: HTD1801 500 mg BID, 1,000 mg BID, or placebo BID. In addition to the subject ID number, subjects will be assigned a randomization number, as well as a kit ID number corresponding to a pre-packaged and numbered study drug kit (see Section 4.1.2).

All subjects and study personnel will remain blinded to the treatment administered throughout the study. All study drugs will be provided in matching white tablets, 4 tablets to a pouch, 2 pouches to be administered each day, 1 pouch in the morning and 1 pouch in the evening. An adequate supply of study drug will be provided to each subject at each clinic visit to cover the next 2- or 4-week period with additional days of coverage, as applicable (e.g., 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 study drug assignment in order to properly treat the subject, the study blind may be broken for that specific subject only. The decision to break the blind for a 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.

3.6 REPLACEMENT OF DROPOUTS

Subjects who do not complete the Double-Blind Treatment Period may be replaced at the Sponsor's discretion.

4.0 STUDY 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 salt and UDCA after oral administration.

4.1.2 Labeling

The study drugs (HTD1801 500 mg, HTD1801 1,000 mg, and placebo) will be supplied by HighTide and packaged into polyethylene terephthalate/aluminum foil/polyethylene (PET/AL/PE) pouches. Each pouch will contain 4 HTD1801 250 mg and/or HTD1801-matching placebo tablets and be affixed with a single-panel label that will describe the following information at a minimum: study drug, dose, kit number, Sponsor name, instructions for storage between 36°F and 46°F (2°C and 8°C), and includes the statements "Caution: New Drug - Limited by United States law to investigational use" and "Keep out of reach of children."

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

4.2 DOSING INSTRUCTIONS AND SCHEDULE

Subjects are instructed to take the entire contents of 1 pouch of study drug each morning and each evening **with water and food (e.g., meal or snack)** during the Double-Blind Treatment Period. Each pouch will contain 4 identical white tablets. Subjects should retain the empty pouches and return them to the investigational site on their next visit

along with any unused study drug. Returned unused study drug must not be re-dispensed to subjects.

4.3 HANDLING OF INVESTIGATIONAL PRODUCT

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

4.4 COMPLIANCE WITH INVESTIGATIONAL PRODUCT

At applicable clinic visits during the Double-Blind Treatment Period (see Section 5.1.3), subjects will be queried about their compliance with taking their assigned study drug as instructed. The number of full and empty study drug pouches will be captured on the electronic case report form (eCRF).

4.5 CONCOMITANT MEDICATIONS

The use of permitted concomitant medications may continue during the study at the same dosage strength and frequency. If subjects are receiving permitted medications, doses and regimens should be stable as described in Section 3.3.1:

- Thiazolidinediones, GLP-1 agonists, DPP-4 inhibitors, or SGLT-2 inhibitors must be stable for ≥90 days prior to randomization;
- Vitamin E dose of ≤400 IU must be stable for ≥90 days prior to randomization with no anticipated dose increases during the study;
- Regimens for other concomitant medications must be stable for ≥28 days prior to randomization.

Changes to permitted concomitant medications are not to be made unless medically necessary. The Medical Monitor may be consulted, as needed, on such changes. The need for medication or dose changes must be documented in the subject's source documents (e.g., in response to an AE).

During the Double-Blind Treatment Period, concomitant medications should not be taken within 1 hour prior to dosing of study drug or up to 6 hours following dosing of study drug.

Note the following for specific concomitant medications:

- Dose adjustments for T2DM medication regimens, including those for metformin and insulin, will primarily be made in consultation with the subject's primary care physician.
- Short courses of oral prednisone/prednisolone (or prednisone/prednisolone equivalent) ≤10 mg/day for conditions unrelated to NASH (e.g., allergic reaction) are permitted.
- The study drug should be taken >1 hour before or 4-6 hours after taking any of the following: bile acid sequestering agents (e.g., cholestyramine and colestipol), aluminum-based antacids (e.g., aluminum hydroxide), or traditional Chinese medicines.
- Based on HTD1801 human PK data and *in vitro* inhibition of cytochrome P450 (CYP450) and uridine diphosphate glucuronosyltransferase (UGT) enzymes, a meaningful inhibition of CYP2D6, CYP3A4, and UGT enzymes at the doses used in this study is not expected. Other than those listed in Section 4.6, Table 4, the concomitant use of statins, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and other antidepressants (i.e., agomelatine, mirtazapine, reboxetine, vilazodone, and vortioxetine) is permitted.

4.6 PROHIBITED CONCOMITANT MEDICATIONS

Certain concomitant medications have been identified for **exclusion** from this study and are not to be taken at any time during the entire study (i.e., from Screening through the Follow-up Period). These exclusions are primarily due to the potential drug interaction profile of the BBR component of HTD1801. Table 4 lists medications known to be strong inhibitors of P-glycoprotein (P-gp), CYP3A4, and CYP2D6; strong inducers of CYP3A4; as well as P-gp substrates with a narrow therapeutic index, and that are prohibited from concomitant use during this study.

Table 4. Prohibited Medications

Single Agents:

P-glycoprotein	CYP3A4		CYP2D6
clarithromycin	clarithromycin	ritonavir	bupropion
erythromycin	telithromycin	saquinavir	fluoxetine
amiodarone	troleandomycin	telaprevir	fluvoxamine
digitalis	nefazodone	tipranavir	paroxetine
dronedarone	St. John's wort	chloramphenicol	quinidine
carvedilol	itraconazole	rifampin	terbinafine
propafenone	ketoconazole	cobicistat	
quinidine	posaconazole	grapefruit juice	
ranolazine	voriconazole	conivaptan	
verapamil	atazanavir	diltiazem	
sildenafil	boceprevir	idelalisib	
itraconazole	darunavir	enzalutamide	
ketoconazole	indinavir	mitotane	
ritonavir	lopinavir	carbamazepine	
saquinavir	nelfinavir	phenytoin	
telaprevir			
lapatinib			

Combination Agents:

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

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

The Investigator should consult the Medical Monitor, as needed, on the concomitant use of any additional medications.

4.7 MANAGEMENT OF CONCOMITANT CONDITIONS

In general, the Investigator should advise subjects to consult their primary care physician as medically warranted.

Specifically for the management of T2DM, the Investigator will instruct study subjects to visit or consult their primary care physician if clinical laboratory results or other symptomatology indicate a hypoglycemic or hyperglycemic state. The Investigator will advise subjects on routine blood glucose monitoring and follow-up with their primary care physician, consistent with the subjects' standard T2DM management practices, as well as instruct subjects to report any signs or symptoms of low or high blood glucose for appropriate management and follow-up.

4.8 LIFESTYLE CONSIDERATIONS

All subjects will receive a hand-out of standard recommendations about lifestyle modification, including, but not limited to: dietary modification, weight loss, exercise, the use of dietary supplements, and alcohol consumption. Subject adherence to diet and lifestyle recommendations will not specifically be assessed.

5.0 EXPERIMENTAL PROCEDURES

5.1 PROCEDURES, MEASUREMENTS, AND EVALUATIONS

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

Throughout the study, clinical laboratory (blood and urine) samples will be collected during a fasting state (i.e., at least 8 hours prior to sample collection) and sent to the designated central laboratory for analysis. Study drug should be taken with water and food (e.g., meal or snack).

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

5.1.1 Screening (Days -28 to -1)

Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. Screening procedures must be completed within 28 days prior to the Baseline visit and can be performed across multiple days during this period. Screening clinical laboratory tests (see Sections 6.2.2 and 6.3.4) may be repeated **once** during Screening if the Investigator believes the results to be erroneous. In the event that Screening tests are repeated, the most current results will be used to determine eligibility. Potential subjects who do not meet all eligibility criteria at Screening will be allowed to re-screen **once** if the Investigator believes that there has been a change in eligibility status. If a potential subject fails to meet eligibility criteria upon re-screen, he/she will remain ineligible for the study.

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

- Informed consent
- Confirm eligibility criteria
- Demographic information
- Medical history
- Comprehensive physical examination
- Vital signs
- Weight and height
- 12-lead ECG
- Serum chemistry panel
- Lipid panel
- Hematology with differential
- Coagulation panel
- HbA1c
- HIV and Hepatitis B/C
- G6PD
- Serum pregnancy test (for FOCP)
- FSH test (for postmenopausal females)
- Urine drug test
- MRI-PDFF
- Corrected T1 and T2*
- AEs
- Prior and concomitant medications

Potential subjects who have successfully completed all of the Screening procedures and who have met all the eligibility criteria (see Sections 3.3.1 and 3.3.2) will be eligible for enrollment in the study. Eligible subjects will be instructed to stop all prohibited medications (see Section 4.6) prior to beginning Baseline procedures.

5.1.2 Baseline (Day 0)

Prior to randomization, potential subjects will undergo the following Baseline procedures and assessments:

- Updated medical history
- Targeted physical examination
- Vital signs
- Weight
- 12-lead ECG
- Urine pregnancy test (for FOCP)
- Updated prior and concomitant medications
- AEs that have occurred since signing informed consent

If potential subjects continue to satisfy the eligibility criteria based upon the procedures and assessments stated above, those data will become part of the Baseline visit. Those potential subjects may then be randomized and officially become subjects in the study. 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.

Prior to dosing, the following additional Baseline procedures and assessments will be conducted at the investigational site. The 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 include:

- Serum chemistry panel
- Lipid panel
- Hematology with differential
- Coagulation panel
- HOMA-IR
- Serum pregnancy test (for FOCP)
- Pro-C3
- ELF test
- Bile acid panel

Following the successful completion of all Baseline procedures, the subject will self-administer the first dose of the study drug, consisting of 4 tablets (1 pouch), under the supervision of investigational site staff. A 2-week supply of study drug will be dispensed to the subject to take home, and the dosing instructions and schedule will be provided (see Section 4.2). 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, 6, 10, 14, 18)

During the Double-Blind Treatment Period, the following procedures and assessments will be conducted during the visits to the investigational site on:

Week 2 –

- Weight
- Serum chemistry panel
- AE monitoring
- Concomitant medications

Weeks 6 and 14 –

- Targeted physical examination
- Vital signs
- Weight
- 12-lead ECG
- Serum chemistry panel
- AE monitoring
- Concomitant medications

Week 10 –

- Weight
- Serum chemistry panel
- Lipid panel
- Hematology with differential
- Coagulation panel
- HbA1c
- Bile acid panel
- AE monitoring
- Concomitant medications

Week 18 –

- Comprehensive physical examination
- Vital signs
- Weight
- 12-lead ECG
- Serum chemistry panel
- Lipid panel
- Hematology with differential
- Coagulation panel
- HbA1c
- HOMA-IR
- Serum pregnancy test (for FOCP)
- MRI-PDFF
- Pro-C3
- ELF test
- Bile acid panel
- AE monitoring
- Concomitant medications

Note: The serum chemistry panel performed at the Week 2, Week 6, and Week 14 visits only includes testing of alkaline phosphatase (ALP), ALT, AST, gamma-glutamyl transferase (GGT), total bilirubin, direct bilirubin, and fasting glucose. The Week 10 and Week 18 bile acid panel applies only to subjects who have had the Baseline bile acid panel performed. Refer to Table 1 and Table 2 for the clinical laboratory collection schedule and corresponding analytes, respectively.

At the completion of the Weeks 2, 6, 10 and 14 clinic visits, the next 4-week supply of study drug will be dispensed to the subject. At all visits, used and unused study drug pouches will be collected from the subject; compliance with taking the study drug will be assessed.

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.

The subject is to be queried for any changes to existing AEs or any additional AEs that may have occurred during the intervening period.

5.1.4 Study Discharge

Following the successful completion of all procedures at the Week 18 visit of the Double-Blind Treatment Period, all subjects are to undergo study discharge procedures. This will include instructions to the subject to contact the investigational site immediately if any problems or concerns arise during the next 30 days of follow-up (see Section 5.1.6).

5.1.5 Early Termination

Should a subject permanently discontinue taking his/her assigned study drug, an Early Termination (ET) visit should be performed. The ET visit procedures and assessments are the same as those performed at the Week 18 visit (see Section 5.1.3). If the ET visit coincides with a regularly scheduled study visit, the ET visit procedures and assessments will be performed in its place. The subject will then be instructed to contact the investigational site immediately if any problems or concerns arise during the next 30 days of follow-up (see Section 5.1.6).

5.1.6 Follow-up Period

All subjects will undergo follow-up evaluations at least 30 days after the last dose of study drug. The follow-up can be via telephone, provided that the subject 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 telephone (or other) contact:

- 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 CONDUCT OF STUDY PROCEDURES AND ASSESSMENTS

For all study procedures and assessments described in this section, refer to the Schedule of Time and Events (Table 1) and Section 5.0.

6.1 ADMINISTRATIVE PROCEDURES

6.1.1 Demographics and Medical History

The Investigator or qualified designee will obtain demographic data, medical history, and medication history for each potential subject at Screening. Demographic data will include, at a minimum, the subject's age and/or date of birth, sex, race, and ethnicity. Medical and medication history will include relevant medical conditions and treatments, including surgical procedures, within the last 10 years of Screening that the Investigator considers clinically significant.

6.1.2 Randomization and Study Drug Management

Upon confirmation of subject eligibility at the Baseline visit (see Section 5.1.2), investigational site staff will login to the designated automated system to randomize the subject and to dispense the assigned study drug kits. The designated automated system will also be used throughout the study to enter study visit data, update the subject's study disposition, and for study drug supply management. Refer to the SPM or applicable instructions for further system and process related details.

6.1.3 Subject Reminder Cards

Subject reminder cards will be provided to all (potential) subjects at each study visit. The reminder cards will inform the subject of the date and time of his/her next scheduled visit and will include any necessary instructions.

6.2 EFFICACY ASSESSMENTS

6.2.1 Magnetic Resonance Imaging

Magnetic resonance imaging-estimated proton density fat fraction will be utilized as the primary efficacy measure to quantify LFC. Proton density fat-fraction, which is a fundamental property of tissue that measures hepatic fat concentration based on the

density of mobile protons from fat (triglycerides) compared to the total density of protons from mobile triglycerides and mobile water, is well-accepted as a standardized non-invasive biomarker of LFC (Reeder et al., 2012).

Corrected T1 (or iron-corrected T1) is an MRI-based technique that characterizes tissue *in vivo* based on the fluidity of water protons within the tissue. Relative to liver tissue, the T1 measurement of free water increases with inflammation and fibrosis, but must be corrected due to the confounding effect of iron (Banerjee et al., 2014). While cT1 will not be utilized as an efficacy measure for this study, it will be utilized as a biomarker of fibrosis to qualify potential subjects given its reported correlation with histological parameters of liver disease (Pavlides et al., 2016).

Investigational sites will utilize their local MRI facility, which will be qualified according to a study-specific image acquisition protocol, to acquire the MRI-PDFF and cT1 scans. Magnetic resonance imaging scans will be performed on the subjects' abdominal region and will last approximately 10 minutes. Scan data will then be transmitted electronically via a secure portal to a central imaging laboratory for analysis. Central imaging specialists blinded to the clinical data will use the *Liver*MultiScan *Discover*™ (LMSD; Perspectum Diagnostics, Oxford, United Kingdom) investigational device to analyze the scans and report the MRI-PDFF, cT1, and T2* results to the investigational sites. The MRI-PDFF, cT1, and T2* results will be reported at Screening, with MRI-PDFF and cT1 as part of the eligibility criteria. At a minimum, clinical metrics for the MRI-PDFF will be reported at the Week 18 or ET visit. Technical and analysis specifications and procedures, including the blinded reporting of any results, will be detailed in the central imaging manual, imaging charter, and/or SPM.

6.2.2 Efficacy Related Laboratory and Biomarker Assessments

A central laboratory will be utilized to perform efficacy related clinical laboratory and biomarker assessments as specified in Table 1 and Table 2 and as described in this section. Samples for laboratory and biomarker assessments performed at Baseline must be collected **prior to study drug dosing**. The Investigator or qualified designee must review the results of all central laboratory testing to assess subject eligibility at Screening and Baseline, as well as continued study participation for the duration of the Double-Blind Treatment Period. Procedures for sample collection and handling,

including the blinded reporting of any results, will be detailed in the central laboratory manual and/or SPM.

The following laboratory and biomarker assessments will be utilized as secondary efficacy measures:

Fasting glucose, HbA1c, HOMA-IR, serum triglycerides, LDL-c, and HDL-c will be utilized in this study to assess glucose metabolism, insulin resistance, and lipid metabolism. These measures are routinely performed in the management of metabolic abnormalities that underlie the pathogenesis of NAFLD, including dyslipidemia and T2DM, the latter of which is recognized as a risk factor for progressive hepatic fibrosis (Adams and Angulo 2006).

Aspartate aminotransferase and ALT are liver-associated enzymes that will be utilized in this study to assess liver biochemistry. These enzymes are markers of liver injury that may be useful surrogate measures of NAFLD and NASH, particularly in T2DM patients (Sanyal et al., 2015).

Pro-C3 and the ELF score are biomarkers that will be utilized in this study to assess liver inflammation and fibrosis. Pro-C3 is a neo-epitope of PIIINP, which has been reported to reflect the true formation of collagen and to potentially be an accurate biomarker for the formation of fibrotic tissue in the liver (Nielsen et al., 2013). The ELF score is a set of extracellular matrix markers that consists of TIMP-1, PIIINP, and HA, and has been reported to show good correlations with fibrosis stages in chronic liver disease (Lichtinghagen et al., 2013).

Total bile acids, C4, and FGF19 are biomarkers that will be utilized in this study to assess bile acid homeostasis. Factors implicated in the pathogenesis of NASH, such as obesity or increased BMI, insulin resistance, and elevated AST and ALT serum concentrations to the dysregulation and increase of serum bile acids. Likewise, elevations in serum C4, an indicator of bile acid synthesis *in vivo*, have been observed in NASH patients. Conversely, reduced serum concentrations of FGF19, which inhibits the rate-limiting enzyme CYP7A1 to regulate bile acid synthesis, have also been observed in NASH patients (Zhang and Deng 2018). Furthermore, the results of a recent study of BBR administered to wild type and farnesoid X receptor (FXR)

knockout mice suggest that BBR may exert its lipid-lowering effect by modulating bile acid turnover and activating the FXR-FGF19 signaling pathway (Sun et al., 2017).

6.3 SAFETY ASSESSMENTS

6.3.1 Physical Examinations

Physical examinations must be performed at investigational sites by medically qualified individuals according to local requirements. Abnormal physical examination findings that the Investigator considers clinically significant are to be reported as AEs.

The comprehensive physical examination will include the assessment of the following: skin; head, neck, eyes, ears, nose, throat; upper and lower extremities; chest and lungs; abdomen; cardiovascular system; and a brief neurological examination. The targeted physical examination will be a symptom-driven assessment of body systems or organs as indicated by AEs or other findings.

6.3.2 Vital Signs, Height, and Weight

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

6.3.3 Electrocardiograms

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

6.3.4 Safety Related Laboratory Assessments

A central laboratory will be utilized to perform safety related clinical laboratory assessments as specified in Table 1 and Table 2 and as described in this section. Samples for laboratory assessments performed at Baseline must be collected **prior to study drug dosing**. The Investigator or qualified designee must review the results of all central laboratory testing to assess subject eligibility at Screening and Baseline, as well as continued study participation for the duration of the Double-Blind Treatment Period. Procedures for sample collection and handling, including the blinded reporting of any results, will be detailed in the central laboratory manual and/or SPM.

In addition to standard serum chemistry, lipid, hematology, and coagulation panels (see Table 2) conducted at specific visits throughout the study, samples to assess HIV and Hepatitis B/C, G6PD, and recreational drug use will only be collected at Screening to determine those factors that could render the subject unsuitable for the study or confound study results.

A local laboratory will perform serum pregnancy testing at Screening, Baseline, and at the Week 18 visit for all FOCP. A locally performed urine pregnancy test will also be done at Baseline. A local laboratory will perform FSH testing at Screening for all postmenopausal females.

6.3.5 Adverse Events

Adverse events will be collected from the time at which the potential subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study until at least 30 days after discontinuing the study drug. General and non-leading questions such as “How are you feeling?” should be asked when assessing the occurrence of AEs. The definition, reporting, and recording requirements for AEs are described in Section 7.0.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be reviewed to determine study eligibility for potential subjects and to monitor continued study participation. In addition to medication history (see Section 6.1.1), any medication, including prescription, over-the-counter, or natural/herbal preparations, received within 28 days of

randomization and the first dose of study drug through at least 30 days after discontinuing the study drug must be recorded in the eCRF. Changes to medication doses or regimens, e.g., in response to an AE, must also be recorded in the eCRF. See Sections 4.5 and 4.6 for details on non-prohibited and prohibited medications.

7.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.1 DEFINITION OF AN ADVERSE EVENT

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

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

The following are examples of AEs:

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

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

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g., endoscopy, appendectomy). The medical condition that led to the procedure as the AE should be reported.

- Situations that are unwanted by the subject but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital.

- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall.

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

Adverse events may include 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).

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

The Investigator is responsible for all AE assessments. The Investigator and investigational site staff will note all AEs mentioned by the subject at Baseline and during study drug administration. All clinical complaints volunteered by or elicited from the subject during the study will be recorded on the appropriate page of the eCRF for the study period indicated (see Section 6.3.5). 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. Serious adverse events require special reporting in addition to documentation in the eCRF as described in Section 7.7.

7.2 DEFINITION OF A SERIOUS ADVERSE EVENT

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

- Results in death.
- Is life-threatening. The term life-threatening in the definition of an SAE refers to an event in which the subject was at risk of death at the time of the event. The term life-threatening does not refer to an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or a prolongation of an existing hospitalization. In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs, but not necessarily SAEs. A medical occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatments of a preexisting condition that did not worsen from its original Baseline level is not considered an SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions. This does not include AEs of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- A congenital anomaly or birth defect. This refers to the offspring of a study subject.
- 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).

7.3 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 Sponsor's or designee's 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. Adverse events being processed as SAEs will also require additional documentation. The SPM (or other applicable instructions) provides additional guidelines about reporting SAEs.

7.4 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 judgment. The classifications in Table 5 should be used in assigning intensity of each AE recorded in the eCRF.

Table 5. Classification of AEs by Intensity

Intensity[a]	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

[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, an AE itself may be of relatively minor medical significance, such as a severe headache. Both AEs and SAEs can be assessed as severe. An AE is considered serious when it meets one of the predefined outcomes described in Section 7.2.

7.5 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 a criterion used to determine regulatory reporting requirements and should not be left blank on the eCRF. The same applies to AEs that are to be processed as SAEs.

Table 6 provides some definitions to use in the assessment.

Table 6. 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.

7.6 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.

7.7 REPORTING OF SERIOUS ADVERSE EVENTS

1. Any SAE occurring after the subject signs the ICF and the study drug has been administered, as described in Section 7.1, must be reported to the Sponsor's or designee's pharmacovigilance department by phone, fax, or e-mail within 24 hours of the time the Investigator becomes aware of the SAE (Table 7). Any SAE reported by phone should be immediately followed up with the submission of the completed SAE report form. Urgent reporting of SAEs is required for the following reasons:

    a. To enable the Sponsor to fulfill the reporting requirements to the appropriate regulatory authority;

b. To facilitate discussion between the Sponsor and the Investigator about appropriate follow-up measures (if necessary);

c. To facilitate the Sponsor's rapid dissemination of information about AEs to other investigators or sites in a multicenter study;

d. To facilitate reporting unanticipated problems involving risk to subjects to the institutional review board (IRB) or independent ethics committee (IEC).

Table 7. Timeline for Reporting SAEs

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

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

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

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

7.8 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 considered not causally related to investigational product;
- The subject is lost to follow-up;
- The subject is followed for at least 30 days after the last dose of study drug (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 also will 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 Sponsor's or designee's pharmacovigilance department as outlined in Table 7.

7.9 LIVER ADVERSE EVENTS

The algorithm (Chalasani and Regev 2016) described in Table 8 will be used to monitor for drug-induced liver injury (DILI).

Table 8. Algorithm to Monitor for DILI

Treatment Emergent ALT	Treatment Emergent Total Bilirubin (TB)	Liver Symptoms	Actions
Normal Baseline: ALT >2x ULN	Normal	None	• Repeat ALT, AST, ALP, TB, in 2-5 days after receipt of the scheduled ALT results (Table 1). • Follow up for symptoms.
Elevated Baseline: ALT >2x Baseline or >300 U/L (whichever occurs first)	Patients with Gilbert's syndrome: No change in Baseline TB		

Treatment Emergent ALT	Treatment Emergent Total Bilirubin (TB)	Liver Symptoms	Actions
Normal Baseline: ALT >5x ULN	Normal	None	• Interrupt study drug. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Elevated Baseline: ALT >5x Baseline or >500 U/L (whichever occurs first)	Patients with Gilbert's syndrome: No change in Baseline TB		
Normal Baseline: ALT >2x ULN	TB >2x ULN	None	• Interrupt study drug. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Elevated Baseline: ALT >2x Baseline or >300 U/L (whichever occurs first)	Patients with Gilbert's syndrome: Doubling of direct bilirubin		
Normal Baseline: ALT >2x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	• Interrupt study drug. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Elevated Baseline: ALT >2x baseline or >300 U/L (whichever occurs first)	-		

Note: Baseline is the average of the Screening and Baseline visit ALT measurements.

As described in Table 8, close monitoring of the subject must be initiated if certain signals of a possible DILI are detected. At a minimum, close monitoring includes:

- Repeating liver enzyme and serum bilirubin tests 2-3 times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or if the study drug has been discontinued and the subject is asymptomatic.

- Obtaining a more detailed history of the subject's symptoms and prior or concurrent diseases.

- Obtaining a history of the subject's concomitant medication use (including non-prescription medications and herbal/dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.

- Obtaining a history of the subject's exposure to environmental chemical agents.

- Obtaining additional tests to evaluate the subject's liver function, as appropriate (e.g., INR, direct bilirubin).

- Considering gastroenterology or hepatology consultations.

At a minimum, the Medical Monitor should be consulted on events that may be considered DILI. Rechallenge is not recommended if it is determined that the subject has experienced DILI.

7.10 PREGNANCY

When any member of the investigational site staff becomes aware of a subject's (or subject's partner's) pregnancy, the site staff must report the pregnancy to the Sponsor's or designee's pharmacovigilance department within 24 hours by using the Pregnancy Notification Form. The female subject will discontinue study drug. The pregnancy will be followed until there is an outcome and the outcome is reported to the Sponsor. Pregnancy is not to be reported as an AE.

7.11 DATA AND SAFETY MONITORING BOARD

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including 2 physicians and a statistician. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The composition of the DSMB, procedures, meeting frequency, and operating guidelines will be detailed in a separate DSMB charter. Each data element that the DSMB needs to assess or be informed of will also be clearly defined in the DSMB charter.

8.0 STUDY OR SITE TERMINATION AND SUBJECT DISCONTINUATION

8.1 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. The Investigator should consult the Medical Monitor, when possible, for any situations (e.g., abnormal, clinically significant findings) that may result in a change to the subject's treatment or management.

8.2 NONCOMPLIANCE

After the Investigator, the Medical Monitor, and/or Study Monitor consult (and the Sponsor, if appropriate), a subject may be discontinued from the study for the following administrative reasons:

- Failure to take the assigned study drug as mandated by the instructions provided in Section 4.2.
- Failure to comply with protocol requirements.
- Unauthorized, subject-initiated changes in the study drug dosing regimen.

8.3 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 AE. If a subject withdraws before completion, every effort should be made to complete the ET visit and follow-up assessments (see Sections 5.1.5 and 5.1.6). A subject may be removed from the study for the reasons described in Section 8.1 through Section 8.3.

8.4 PREMATURE STUDY OR SITE TERMINATION

If the Sponsor, Investigator, Medical Monitor, Study Monitor, and/or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the investigational site should be terminated, this action may be taken after appropriate consultation among the Sponsor, Investigator, Medical Monitor, and/or Study Monitor. The Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, will be used for assessment of trial stopping criteria.

The study 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 investigational product.

A study conducted at a single investigational 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 investigational site to the Sponsor, Study Monitor, or appropriate regulatory authority;
- Insufficient adherence to protocol requirements.

Study termination and follow-up will comply with conditions set forth in ICH E6, Guideline for Good Clinical Practice (GCP), Sections 4.12, 4.13, 5.20, and 5.21.

9.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

9.1 DATA COLLECTION AND PROCESSING

Electronic case report forms will be used to capture study assessments and data. The study coordinator or other delegated study staff at the investigational site 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 eCRFs 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 at the investigational site 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 investigational 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 ID and password before any data can be entered in the eCRFs. Authorized study staff at the investigational site 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 10.2.

9.2 STATISTICAL ANALYSIS

9.2.1 General Overview

The study analyses will be conducted in a GCP controlled environment and will be described in detail in a Statistical Analysis Plan (SAP). The SAP will also include the analysis table, listing, and figure specifications.

A Biostatistics Data Review Meeting will be conducted to prior to database lock in order to determine which protocol deviations are major vs. minor.

The data will be summarized in tables and listings according to nominal study visit and treatment group. As appropriate, tables will display the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. All statistical analyses will be performed and data appendices will be created by using SAS (version 9.2 or later, Cary NC).

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

No alpha adjustments for multiplicity will be made for analysis of efficacy endpoints for this POC study.

9.2.2 Analysis Datasets

The efficacy dataset will consist of all randomized subjects who meet the following conditions:

- For analysis of the primary efficacy endpoint, randomized subjects who complete at least 80 days of study drug dosing and have a Week 18 (or ET) visit MRI-PDFF assessment.
- For analysis of the secondary efficacy endpoints, randomized subjects who receive at least one dose of study drug and have at least one post-dose assessment.

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

9.2.3 Efficacy Analysis

9.2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change from Baseline to Week 18 in LFC, or absolute change from Baseline to the ET visit for subjects who terminate the study prematurely. Absolute change from Baseline in LFC will be assessed by analysis of covariance that includes the effects of treatment group, Baseline LFC, and Baseline ALT. Comparison of each active treatment group to placebo will be tested at the 5% level of significance without adjustment for multiple tests. Secondarily, comparison of the 2 active treatment groups with each other will be tested at the 5% level.

9.2.3.2 Secondary Efficacy Endpoints:

The secondary efficacy endpoints of this study include the following:

1. Absolute and relative (percent) change in fasting glucose and HbA1c from Baseline to Week 18, or to the ET visit for dropouts.
2. A ≥30% reduction in LFC from Baseline to Week 18, or to the ET visit for dropouts.
3. Percent change in LFC from Baseline to Week 18, or to the ET visit for dropouts.
4. Normalization of LFC to <5% at Week 18, or to the ET visit for dropouts.
5. A ≥5-percentage point reduction in LFC from Baseline to Week 18, or to the ET visit for dropouts.
6. Absolute and percent change in HOMA-IR from Baseline to Week 18, or to the ET visit for dropouts.
7. Absolute and percent change in LDL-c, serum triglycerides, and HDL-c from Baseline to Week 18, or to the ET visit for dropouts.
8. Absolute and percent change in AST and ALT from Baseline to Week 18, or to the ET visit for dropouts.

9. Normalization of ALT (according to clinical laboratory reference ranges) to Week 18, or to the ET visit for dropouts, among subjects with elevated ALT at Baseline.

10. Absolute and percent change in Pro-C3 from Baseline to Week 18, or to the ET visit for dropouts, among subjects with elevated Pro-C3 at Baseline.

11. Absolute and percent change in the ELF score and each component of ELF (TIMP-1, PIIINP, and HA) from Baseline to Week 18, or to the ET visit for dropouts.

12. Absolute and percent change in total bile acids, C4, and FGF19 from Baseline to Week 18, or to the ET visit for dropouts.

Percent change from Baseline in LFC will be analyzed by the same model described for the primary efficacy endpoint. Normalization of LFC, a ≥30% reduction in LFC, and a 5-percentage point reduction in LFC will each be analyzed by a logistic regression that includes the effects of treatment group, Baseline LFC, and Baseline ALT.

All additional secondary efficacy endpoints are continuous and each will be assessed by analysis of covariance that includes treatment group and the Baseline value of the analysis variable. All secondary analyses (except LFC) will have missing Week 18 values imputed using a multiple imputation procedure for all subjects with an available measurement prior to Week 18.

9.2.4 Missing Data

It is unlikely that all subjects will complete the 18-week evaluation. Endpoints that will only be measured at Week 18 or the ET visit (i.e., LFC) will have the value at the ET visit imputed for the missing Week 18 visit. All other efficacy endpoints will have their Week 18 value imputed using a multiple imputation procedure.

9.2.5 Safety Analysis

The safety dataset will be used for all safety analyses. Safety analyses will address AEs, physical examinations, vital signs, ECGs, and clinical laboratory assessments.

Adverse event type will be coded using MedDRA. Adverse event data will be listed individually; AE incidence will be summarized by system organ class and preferred terms within a system organ class for each treatment group. Adverse event type, relationship, severity, onset, and duration will be presented by treatment group within the Double-Blind Treatment Period. Liver-specific AEs also will be included.

The number of subjects with AEs, as well as the number of AEs, also will be displayed. At the subject-level, each AE will be counted only once for a given subject within a specified system organ class, preferred term. If the same AE occurs on multiple occasions for a subject, the occurrence with the highest severity and relationship to study medication will be reported. Individual AE terms will be reported as separate events.

Changes in vital signs, ECGs, and clinical laboratory parameters from Baseline to end of study will be examined and displayed using shift tables (low, normal, high). Shift tables for Week 18, or the last available study visit, will be presented relative to Baseline for all clinical laboratory parameters.

9.2.6 Sample Size

An absolute change in LFC of 5% as measured by MRI-PDFF has been reported to be the minimal clinically relevant difference between active treatment and placebo that correlates with histological improvement in NASH (Loomba et al., 2015, Patel et al., 2015). Furthermore, Harrison and colleagues reported a pooled standard deviation of 6.3% for changes from Baseline in LFC (Harrison et al., 2018). Based on this standard deviation, 35 subjects in each treatment group will provide 90% power to show a difference of 5 percentage points between any 2 treatment groups at the 5% level of significance. To allow for a dropout rate of 10%, 39 subjects will be randomized to each of the 3 treatment groups.

9.2.7 Interim Analysis

An interim analysis will be conducted after a minimum of 51 subjects complete the assessment of the primary efficacy endpoint to assess sample size assumptions and futility through conditional power; the study will not be stopped for efficacy. The method of Cui and colleagues (Cui et al., 1999) will be used to compute the alpha spend

associated with the interim analysis to assess futility and to recompute sample size by evaluating the pooled standard deviation for the change from Baseline in LFC.

Conditional power calculations will be performed for the difference between each of the 2 active treatment groups versus placebo for the primary endpoint. The following rules will be applied for the primary efficacy endpoint:

1. If both conditional powers at the time of the interim analysis are <10%, then the study will be terminated for futility.

2. If either conditional power is ≥10% but both are <36%, then the sample size will not be increased and the study will continue based on the original sample size.

3. If either conditional power is ≥36% but both are <80%, then the sample size will be adjusted to retain the original power of 90% or a 50% increase in the sample size, whichever is the smallest.

4. If either conditional power is ≥80%, then the study will continue as is.

The Sponsor will be advised of either futility, no change, or of a specific sample size increase, but not about the degree of efficacy per treatment group. The analysis will be conducted by an independent statistician who is not otherwise involved in the operational aspects of this study.

10.0 STUDY ADMINISTRATION

10.1 INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

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

10.2 STUDY DOCUMENTATION

10.2.1 Investigator Information

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

10.2.2 Investigator's Study Files

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

10.2.3 Case Report Forms and Source Documentation

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

10.2.4 Retention of Study Documents

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

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

10.3 CONFIDENTIALITY

10.3.1 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).

10.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject ID number (see Section 3.5) on eCRFs and other documents retrieved from the investigational site or sent to the Study Monitor, Sponsor, regulatory agencies, central laboratories, or blinded reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the Study Monitor, or Sponsor representatives.

10.4 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 ICF, the revised ICF prepared by the Investigator must also be approved by the Sponsor, Study Monitor, and the IRB/IEC before implementation.

Departures from the protocol eligibility criteria (see Sections 3.3.1 and 3.3.2) are not permitted as these could jeopardize subject safety, study integrity, or regulatory acceptance of the results.

Departures from other protocol procedures or requirements are allowed only in situations that eliminate an immediate risk to a subject and that are deemed crucial for the safety and well-being of that subject. The Investigator or the attending physician will also contact the Medical Monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB/IEC; however, the

IRB/IEC and Medical Monitor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the subject's eCRF the reasons for the protocol deviation and the ensuing events.

10.5 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 ICH E6, Section 5.18.4.

10.6 GENERAL INFORMATION

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

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APPENDICES

APPENDIX A

PROTECTION OF HUMAN SUBJECTS
(International Conference on Harmonisation E6)

PROTECTION OF HUMAN SUBJECTS

(International Conference on 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 ICF. When minors are involved, a parent or guardian should sign the ICF. 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 an ICF written in a language that they understand. A copy of the signed ICF 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 ICF 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 ICF, 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 ICF 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 ICF, 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 or 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 ICF if applicable (to include name, address, and chairperson of the IRB or IEC)
- Blank copy of the IRB or IEC-approved final and revised ICF
- 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 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, IRB/IEC approval of the trial, the protocol, protocol amendments, and changes to the ICF.

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, ICFs, 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; SPM; IRB or IEC approval of protocols, amendments, and ICF; 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 ICH guidelines as defined in ICH E6 Section 3, IRB/IEC

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 ICF 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 ICF 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" ICF (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:

  1. IRB or IEC charter membership and qualifications of each member
  2. IRB or IEC letter of approval of protocol and amendments
  3. IRB or IEC letter of approval of ICF and amendments
  4. Investigator's annual report to the IRB or IEC
  5. IRB or IEC annual re-approval of protocol
  6. Reports to IRB or IEC of deaths and serious adverse events (SAEs)
  7. Notification to IRB of study completion and Investigator's final report
  8. 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:

  1. Subject screening log
  2. Medical exceptions log
  3. Site status report
  4. Subject identification code list
  5. Original signed ICF
  6. A note stating the location of the eCRFs and data clarification requests

  – Copies of completed eCRF transmittal logs

- Investigation product records, including the following:

    1. Receipt, date and quantity, and batch or lot number

    2. Disposition dates and quantity administered to each subject

    3. Inventory records

    – All correspondence related to the investigational product

- SAE/safety reports

    1. Copies of signed SAE reports

    2. All SAE correspondence, including MedWatch and Form FDA 3500A

- Biological sample inventory forms and correspondence with the analytical laboratory

- Monitoring activities

    1. Monitoring log (should include all visits [i.e., site initiation, periodic, and termination visits])

    2. Telephone contact reports

    3. Site initiation visit reports

- General Correspondence

    1. All correspondence between the Study Monitor, Sponsor, and the site

    2. 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.