CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

A Randomized, Double Blind, Placebo Controlled, Multicenter, Multiple Ascending Dose Study to Evaluate the Safety and Tolerability of HTD1801 in Adults with Hypercholesterolemia

Protocol Number: 1801.PCT004

Version number: 2.0

Date of issue: 19 January 2018

Sponsor:

HighTide Biopharma Pty Ltd
1 Melissa Street
Mount Waverley, Vic 3149
Australia

Sponsor Protocol Approval

Steven E. Linberg, Ph.D.
Chief Product Development Officer
HighTide Biopharma Pty., Ltd.

Signature **Date**

Chong Ho, Ph.D.
Director
HighTide Biopharma Pty Ltd

Signature **Date**

Document History

Version	Revision Date	Revision Description
1.0	12 Dec 2017	Initial Release
2.0	19 Jan 2018	Amendment 1

STUDY SUMMARY

Protocol Title	A Randomized, Double Blind, Placebo Controlled, Multicenter, Multiple Ascending Dose Study to Evaluate the Safety and Tolerability of HTD1801 in Adults with Hypercholesterolemia
Primary Objective and Endpoints	The primary objective for this study is to assess the safety and tolerability of multiple ascending dose levels of HTD1801 in participants with hypercholesterolemia. Safety assessments will occur throughout the duration of the trial, including monitoring of adverse events (AEs), clinical laboratory tests, vital signs measurements, electrocardiogram, and physical examinations.
Secondary Objectives and Endpoints	There are four secondary pharmacokinetic (PK) and pharmacodynamic (PD) objectives for this study. 1. To assess the PK profile of HTD1801 after repeat doses as assessed by derived PK parameters including but not limited to: • Plasma half-life of HTD1801 components ($t_{1/2}$). • Maximum plasma concentration of HTD1801 components (C_{max}). • Minimum plasma concentration of HTD1801 components (C_{min}). • Time to C_{max} (T_{max}). • Time to C_{min} (T_{min}). 2. To determine the effects of HTD1801 on lipid metabolism: • Fasting lipid metabolism and atherogenic biomarkers as assessed by actual values and change from baseline of: o Low-density lipoprotein-C (LDL-C) o Non-high-density lipoprotein-C (non-HDL-C). o Total cholesterol, high-density lipoprotein-C (HDL-C), and the ratio of total cholesterol to HDL-C. o Apolipoprotein B (ApoB) and A-1 (ApoA1). o Triglycerides and free fatty acid (FFA). o C-reactive protein (CRP) measured using a high-sensitivity assay. o Lipoprotein(a) (Lp(a)). 3. To determine the effects of HTD1801 on glucose metabolism: • Glycosylated hemoglobin (HbA1c) levels. • Markers of fasting glucose metabolism as assessed by actual values and change from baseline of: o Fasting plasma glucose (FPG). o Fasting serum insulin. o C-peptide 4. To determine the effects of HTD1801 on biomarkers of liver function • Actual values and change from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST).
Phase of Development	Phase 1b/2a
Number of Participants	This trial will enroll 48 participants in three planned dose escalation cohorts. Participants who withdraw from the trial for reasons other than safety and tolerability, may be replaced after discussion between the Investigator and Sponsor.

Inclusion Criteria	Participants meeting all the following criteria will be eligible to participate in this trial: 1. Have given written informed consent 2. Males or females aged 18 to 70 years old at the time of first dosing 3. Satisfy the following: Females: Non-pregnant and non-lactating; surgically sterile, post-menopausal, or abstinent; or if engaged in sexual relations of childbearing potential, participant agrees to use two acceptable methods of contraception for 4 weeks prior to the treatment period, for the 4 weeks of the Treatment Period, and for at least 2 weeks after the last dose of study drug. One of the methods must be an appropriate hormonal contraceptive (stable for at least 4 weeks prior to treatment), and the other method can be an acceptable method of barrier contraception, e.g., a condom for the male partner. Males: Surgically sterile or abstinent; or if engaged in sexual relations of childbearing potential, the participant and his partner must agree to use an acceptable contraceptive method during the 4 weeks of the Treatment Period and for 2 weeks after the last dose of study drug. 4. Have a body mass index (BMI) of >25.0 and ≤ 45.0 kg/m^2 at Screening 5. Have a documented history of hypercholesterolemia, defined as LDL-C ≥ 2.59 mmol/L.
Exclusion Criteria	Participants meeting any of the following criteria will be excluded from this trial: 1. The use of any anti-dyslipidemia agent within 28 days prior to dosing 2. History of a total cholesterol ≥ 10.35 mmol/L or triglyceride ≥ 11.3 mmol/L 3. History of a clinically significant cardiac arrhythmia or clinically significant abnormal ECG results at Screening 4. Significant peripheral or coronary vascular disease 5. Clinically significant abnormal blood pressure at Screening or Baseline, defined as supine blood pressure ≥160/100 mmHg, or ≤ 90/60 mmHg 6. Primary hypothyroidism (thyroid stimulating hormone [TSH] > upper limit or normal [ULN] and free T4 < lower limit of normal [LLN]), primary subclinical hypothyroidism (screening TSH > ULN and free T4 within normal limits [WNL]), or secondary hypothyroidism (screening TSH < LLN and free T4< LLN) at Screening 7. Glucose-6-phosphate dehydrogenase (G6PD) deficiency 8. History of unstable proliferative retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator 9. Malignancy within 5 years, except for curatively treated basal cell, squamous cell carcinoma of the skin or carcinoma in-situ of the cervix 10. Known history of, or positive test for, human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B 11. Active infection that is currently producing symptoms or in which the causative organism of the disease is rapidly reproducing 12. Current or recent history (verbal report) in last 6 months of drug or alcohol abuse, or consumption of more than 30 g of alcohol (3 standard drinks) per day (for male and female participants) within 4 weeks prior to Screening, or positive urine drug screen for drugs of abuse 13. Clinically significant abnormalities identified during physical examination or from the participant's medical history such as: a. Any history of cardiac insufficiency defined as New York Heart Association (NYHA) Class II to IV b. Angina pectoris within the last 6 months c. Acute myocardial infarction at any time d. Major surgery within the last 3 months

	e. Stroke 14. Treatment with any agent that decreases body weight, actively enrolled in a weight loss program or following a special diet 15. Gastrointestinal conditions that involve malabsorption or inflammation (e.g., ulcerative colitis, Crohn's disease), and recent or past bariatric surgery of any kind 16. Current or recent use of prohibited medications 17. Current outpatient insulin use, or history of outpatient insulin use for more than 2 weeks in the last year 18. Whole blood donation or significant blood loss within 30 days prior to screening or Plasma donation within 14 days prior to the first study drug administration 19. User of any nicotine containing products within the past 6 months 20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator 21. Participation in an investigational drug trial within 30 days prior to dosing or 10 half-lives within the last dose of said investigational drug, whichever is longer 22. The presence of any other conditions, which, in the opinion of the Investigator would make the participant unsuitable for inclusion, or could interfere with the participant participating in or completing the trial.
Summary of Study Design	This is a randomized, double-blind, placebo-controlled, multicenter, multiple ascending dose (MAD) study to evaluate the safety and tolerability, PK, and PD profiles of HTD1801 in overweight to obese adults with hypercholesterolemia. Two study drugs will be administered: (1) the investigational product HTD1801 and (2) matching placebo. There are three planned dose escalation cohorts. Each cohort will consist of 16 participants randomized 3:1 to receive either HTD1801 or placebo. The cohorts will be enrolled sequentially, but may overlap (the next cohort can begin during the Follow-up Period of the prior cohort). The decision to move to the next dose level will be based on safety findings and will not be dependent on establishing preliminary efficacy findings.

Summary of Study Procedures	The trial will consist of the following: • Screening Period, including a 4-week anti-dyslipidemia treatment washout if applicable • Treatment Period (Days 1-28) consisting of an initial inpatient visit, an outpatient period, and a second inpatient visit • Follow-up Period <u>Screening Period</u> All participants must be consented prior to any study-related activities. Screening assessments will include demographics, medical history, physical exam, vital signs, ECG; as well as laboratory assessments including hematology, lipid profile, clinical chemistry, virus screen, G6PD, urinalysis, drug and alcohol screen, and pregnancy tests. All Inclusion and Exclusion criteria must be met prior to the 1st dose of study medication. Eligible participants who are currently taking anti-dyslipidemia agents will need to discontinue those agents for at least 28 days prior to further participation in the trial. <u>Visit 1</u> Participants will undergo baseline measurement of lipid metabolism, liver function, and glucose metabolism biomarkers. PK samples will be collected for the determination of berberine and UDCA. Participants will be treated with the first dose of study drug (active or placebo). The study drug will be administered with a 240-mL glass of water immediately following the morning meal. Only one dose will be administered on Day 1. Participants will remain in-house for at least 24 hours of safety and PK monitoring following study drug administration. On Day 2, twice per day study drug dosing will begin immediately after morning and evening meals. Participants will be discharged on Day 2 after PK and safety assessments, if they are considered stable by the Investigator. Prior to discharge, participants will be given dietary counseling to prepare them for the outpatient period, as well as instructions to continue taking the study drug twice daily following the morning and evening meals. Participants will be instructed to return to the investigational site with their study drug prior to the morning dosing that will occur on Study Day 14. <u>Outpatient Period</u> Participants will continue to take the study drug twice daily following the morning and evening meals during the entire Outpatient Period. There will be one outpatient visit during that time, intended to occur on Day 14, to provide samples for clinical laboratory assessments, safety assessments; and glucose metabolism, lipid metabolism and liver function biomarker assessments. <u>Visit 2</u> Participants will return to the study site on Day 27 ± 3, and the next day will undergo fasting measurements of glucose metabolism, lipid metabolism and liver function biomarkers. PK samples will be collected for the determination of berberine and UDCA. Participants will remain in-house for approximately 36 hours. Participants will be discharged approximately on Day 29 after PK and safety assessments, if they are considered stable by the Investigator. <u>Follow-up Visit</u> A safety Follow-up phone call will occur on Day 42.

<table>
<tr><td>Treatments</td><td>This trial includes three planned dose escalation cohorts. The doses of HTD1801 (active or placebo) to be administered are summarized in the table below.

Table 1. Planned Dose Escalation Cohorts
<table><tr><th>Cohort Number</th><th>Number of Participants Planned</th><th>Dose Regimen</th></tr><tr><td rowspan="2">1</td><td>12</td><td>HTD1801: 500 mg/day (250 mg bid)</td></tr><tr><td>4</td><td>Placebo: 2 tablets/day (1 tablet bid)</td></tr><tr><td rowspan="2">2</td><td>12</td><td>HTD1801: 1000 mg/day (500 mg bid)</td></tr><tr><td>4</td><td>Placebo: 4 tablets/day (2 tablets bid)</td></tr><tr><td rowspan="2">3</td><td>12</td><td>HTD1801: 2000 mg/day (1000 mg bid)</td></tr><tr><td>4</td><td>Placebo: 8 tablets/day (4 tablets bid)</td></tr></table>
Dose escalation criteria will be applied on a per cohort basis and is distinct from early study termination criteria. All dose escalation and stopping decisions will be made following a discussion between the Sponsor and the Investigator. Dose escalations may be stopped at any time by the Sponsor or the Investigator.</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Duration of Participation</td><td>The trial is expected to take approximately 10 weeks for each participant from Screening through Follow-up.</td></tr>
<tr><td>Sample Size Determination</td><td>The sample size of 16 participants per cohort, with 12 receiving HTD1801 and 4 receiving placebo, was empirically determined and consistent with typical sample sizes used for similar studies to assess robust data for safety and PK.</td></tr>
<tr><td>Statistical Methods</td><td>Safety and tolerability of the study drugs will be assessed by collection and review of AEs, laboratory parameters, and vital signs. Safety analysis will also involve examination of the descriptive statistics and individual participant listings for any effects of study treatment on clinical tolerability and safety.

Safety analyses will be detailed in a statistical analysis plan (SAP). Pharmacokinetic assessments will be summarized using descriptive statistics. Assessments for other secondary objectives will be analyzed using descriptive and comparative statistical methods.</td></tr>
</table>

Table 2. SCHEDULE OF TIME AND EVENTS

Study Period►	Screening	Visit 1			Outpatient Period			Visit 2			Follow-up
Study Day► / EVENT▼	-28 to -1	BSLN	1	2	3-13	14 (clinic)	15-26	27	28	29	42
Informed consent	X										
Demographics	X										
Medical history	X	X									
Physical examination	X	X				X		X			
Eligibility criteria	X	X									
Ht., Wt., Vital signs	X	X	X	X		X		X	X	X	
Urine drug /Alcohol breath test	X		X			X		X			
Pregnancy test	X	X				X		X			
G6PD	X										
Hematology	X	X				X			X		
Clinical Chemistry	X	X				X			X		
Lipid Profile	X	X				X			X		
ApoA1, ApoB, Lp(a) and FFA		X				X			X		
Urinalysis	X	X				X			X		
HIV, Hepatitis B, C	X										
TSH and Free T4	X										
LDH		X				X			X		
ECG	X	X	X			X		X	X		
Concomitant medications	X	X	X	X		X		X	X	X	
Dietary counseling	X			X		X					
C-reactive protein		X				X			X		
Liver function biomarkers		X				X			X		
Glucose metabolism biomarkers		X				X			X		
Study Drug Dosing			q.am	bid	bid	bid	bid	bid	q.am		
PK Sampling		X	X	X					X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X

Table 3. Pharmacokinetic Sampling Schedule

▼ **hours pre (-) and post (+) treatment**	**Baseline**	**Day 1**	**Day 28**
	no drug	**q.am**	**q.am**
-18	X		
-12	X		
-6	X		
0 (pre-dose)		X	X
+0.25 (post dose)		X	X
+0.50		X	X
+1		X	X
+2		X	X
+3		X	X
+4		X	X
+8		X	X
+12		X	X
+24		X	X

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACC	American College of Cardiology
AE	Adverse event
AHA	American Heart Association
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BBR	Berberine
bid or b.i.d.	Twice per day
BMI	Body mass index
BMR	Basal metabolic rate
BSLN	Baseline
BUN	Blood urea nitrogen
CDM	Clinical data management
C_{max}	Maximum concentration
CRF	Case report form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DDE	Drug Dictionary Enhanced (WHO DDE)
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic CRF
ED_{50}	Median Effective Dose
FFA	Free Fatty Acid
FPG	Fasting plasma glucose
FPFV	First participant first visit
FSH	Follicle Stimulating Hormone
G6PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
HbA_{1C}	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High Density Lipoprotein Cholesterol
HED	Human Equivalent Dose
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee

IB	Investigator's brochure
ICH	International Council on Harmonization
IP	Investigational Product
IV	Intravenous
kg	Kilogram
lb	Pound
LDL-C	Low Density Lipoprotein Cholesterol
LLN	Lower Limit of Normal
Lp(a)	Lipoprotein(a)
LPLV	Last Participant Last Visit
mg	Milligram
NYHA	New York Heart Association
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PPP	Pharmaceutical Packaging Professionals (IP logistics contractor)
q.am	Once in the morning.
QD or q.d.	Once per day
RBC	Red Blood Cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SMC	Safety Monitoring Committee
SOE	Schedule of events
$t_{½}$	half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
TG	Triglycerides
T_{max}	Time to maximum serum concentration
TSH	Thyroid-stimulating hormone
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
US	United States
USP	Unites States Pharmacopeia
WHO	World Health Organization
WNL	Within Normal Limits

1. INTRODUCTION

1.1 Background

Hyperlipidemia, is defined as the elevation of fasting levels of total cholesterol or low-density lipoprotein cholesterol (LDL-C), which may or may not be associated with elevated levels of triglycerides [Mitchell et al. 2016; Nelson 2103]. While some patients present with familial hyperlipidemia associated with hereditary factors, hyperlipidemia is most often an acquired condition [Nelson 2013]. In a 2009 survey of primary care physicians, hyperlipidemia was the second most common chronic condition (first was hypertension) observed in primary care [Nelson 2013]. Patients with hyperlipidemia are commonly diagnosed with other comorbid conditions including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and non-alcoholic fatty liver disease (NAFLD) [Mitchell 2016; Nelson 2013; NCEP 2002]. Of these, CVD is the leading cause of death in the United States (US) [Nelson 2013].

Reducing LDL-C is the primary treatment goal for patients with hyperlipidemia [NCEP 2002]. LDL-C consists of a single lipoprotein (apolipoprotein B [ApoB]) and typically makes up approximately 60-70% of total serum cholesterol [NCEP 2002]. Comprehensive treatment guidance has been provided by the National Cholesterol Education Program (NCEP)- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel [ATP] III). In 2013, an update was issued, however, the guidance provided by the American College of Cardiology (ACC) and American Heart Association (AHA) (convened as the ATP IV expert panel) was strictly focused on treatment strategies to reduce atherosclerotic CVD. Therefore, the more comprehensive ATP III recommendations are referenced here. While cholesterol levels <2.59 mmol/L are considered "optimal" these levels are also not considered attainable in all patients, in part due to the cost associated with treatment to target levels on a population wide scale [NCEP 2002]. Therefore, the ATP III panel adopted the following tiered recommendation based on the number of preexisting risk factors for CVD:

- Multiple (2+) risk factors → target LDL-C <3.36 mmol/L achieved through lifestyle modification (baseline LDL-C 3.36-4.11 mmol/L) or lifestyle modification and medication (baseline LDL-C ≥4.14 mmol/L).
- 0-1 risk factors → target LDL-C <4.14 mmol/L (<3.36 mmol/L is preferred) achieved primarily through lifestyle modification. Medication should be considered for patients with LDL-C ≥4.91 mmol/L after lifestyle changes.

However, treatment targets are not met in most (61.8-93.8%) patients at high risk for CVD [Mitchell et al. 2016]. Hyperlipidemia patients with existing CVD or diabetes were the least likely to reach treatment goals [Mitchell et al. 2016].

There are currently three classes of drugs commonly used to treat elevated LDL-C levels:

Statins. Statins are the first-line therapy for patients with elevated LDL-C and act by inhibiting HMG CoA reductase to block cholesterol synthesis. They have been shown to have clinical benefits including lowering LDL-C levels, reducing atherosclerosis, reducing triglyceride levels, and anti-inflammatory effects [NCEP 2002]. Statins are generally well tolerated, but are

associated with adverse effects that may not make them suitable for treating every patient. These effects include muscle pain or weakness (7-29% of patients), hepatic toxicity, limited efficacy in patients with heterozygous familial hypercholesterolemia, and increased risk of insulin resistance [NCEP 2002].

Non-Statins: The second class of LDL-C lowering medications are the non-statins including bile acid sequestrants, niacin (also called nicotinic acid), and ezetimibe. Bile acid sequestrants work indirectly to lower LDL-C levels by relieving feedback inhibition on the pathway that converts LDL-C to bile acid [NCEP 2002]. Niacin reduces circulating LDL-C by preventing hepatic lipoprotein synthesis [NCEP 2002], and ezetimibe prevents cholesterol absorption [NCEP 2002]. However, all three compounds have limited LDL-C reducing effects when taken alone and can have significant gastrointestinal side effects [NCEP 2002].

PCSK9 Inhibitors. Finally, elevated LDL-C levels can be treated using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. This class of drugs blocks the cellular uptake and degradation of the LDL surface receptor on hepatocytes, which is enhanced by soluble PCSK9 binding to the LDL receptor. In healthy individuals, the LDL receptor binds to and removes LDL-C from circulation via lysosomal degradation [Rosei and Salvetti 2016; Tavori et al. 2016]. While PCSK9 inhibitors reduce LDL-C levels, they are costly, require repeated injections, and increase the risk of developing T2DM [Rosei and Salvetti 2016].

Given the limitations of the current LDL-C lowering agents on the market, there is an unmet clinical need for LDL-C lowering agents that may benefit patients with familial hypercholesterolemia, patients in whom other LDL-C lowering medications are not sufficient, and patients who are intolerant to statins.

The investigational product (IP), HTD1801, is a novel compound under development to treat hyperlipidemia, and NAFLD/non-alcoholic steatohepatitis (NASH). HTD1801 is an ionic salt of berberine (BBR) and ursodeoxycholic acid (UDCA) (1:1 stoichiometry). BBR and its derivatives are patented for use treating a wide array of conditions including cancer, inflammation, infectious disease, CVD, metabolic disorders, and others [Singh and Mahajan 2013]. BBR use can be traced back to China some 3,000 years ago. BBR is approved for use as an antiseptic in China, Japan, and Taiwan, and marketed as a dietary supplement for managing diabetes and dyslipidemia in the US, Europe, and Canada. Its lipid and glucose lowering effects have been supported in controlled clinical trials [Lan et al. 2015; Dong et al. 2013]. Typical daily dosing is 0.5-1.5 g/day divided over 2-3 doses [Dong et al. 2013]. UDCA is approved to treat cholesterol gallstones and primary biliary cirrhosis in several markets including the US, Japan, and China, although its efficacy in primary biliary cirrhosis has remained somewhat controversial [Zhu et al. 2015]. The approved dosing regimen is 13-15 mg/kg/day divided over 2-4 doses [UrsoForte Product Insert]. Additional composition/formulation details for HTD1801 are provided in the Investigator's Brochure (IB) and Section 5.1.1.

HTD1801 has been shown to reduce LDL-C levels with a mechanism of action (MOA) that is distinct from statins, to improve liver function, and to normalize glucose homeostasis. Please refer to IB for details on MOA. The preclinical and clinical studies supporting the development of HTD1801 are described in more detail in the IB and below in Section 1.3. The clinical

benefits of its components suggest that HTD1801 has the potential to be an integrated lipid management solution for patients with complex metabolic problems (e.g., NAFLD and T2DM).

1.2 Rationale for the Proposed Study

This is a multiple ascending dose study, the safety data from which will complement the safety data from the single ascending dose study. The primary objective is therefore to assess the safety and tolerability of BBR and UDCA when administered concomitantly in the form of HTD1801. An additional objective is to assess the PK profile of UDCA and BBR after repeat-dose administration of HTD1801 in humans.

As summarized in Section 1.3 below, HTD1801 has been shown in preclinical studies to have multiple activities at a cellular level, amongst which its effects on lipid metabolism, glucose metabolism, and liver function have been most robust. The secondary objective of this study is therefore to monitor for activity in these three metabolic areas as a means to inform future development efforts for HTD1801 in dyslipidemia.

1.3 Summary of Pre-Clinical /Clinical Studies

Detailed information pertaining to the pre-clinical and ongoing clinical studies using HTD1801 is provided in the IB. The results from the most relevant studies are summarized in the sections below.

1.3.1 Pre-Clinical Studies in Animal Models

1.3.1.1 Efficacy Study in Golden Hamsters Fed a High Fat Diet

Syrian golden hamsters (n=8/group) were used to examine the effects of HTD1801 treatment on serum and liver lipid levels following consumption of a high fat diet. The hamsters were divided into four treatment groups: (1) normal control – normal chow, (2) model control – high fat diet, no treatment, (3) low dose HTD1801 – high fat diet, treated with 50 mg/kg HTD1801 once daily (QD) for seven weeks, and (4) high dose HTD1801 – high fat diet, treated with 200 mg/kg HTD1801 QD for seven weeks. At the end of the treatment period, the hamsters were sacrificed and the effects of HTD1801 treatment on serum and liver lipid profiles were assessed. As expected, the hamsters in model group developed significantly higher serum LDL-C and total cholesterol compared to the normal control group. Compared to the normal control group, the serum PCSK9 levels of model group significantly increased. The animals in model group also developed signs of impaired liver function (elevated aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), elevated liver lipids (total cholesterol and triglycerides), and signs of liver inflammation compared to the normal control group. Treatment with HTD1801 significantly reduced serum total cholesterol, triglycerides, and LDL-C, and reduced total cholesterol and triglycerides in the liver in a dose dependent manner. Secondary effects included: reducing the levels of AST and ALT; reducing serum PCSK9 levels; improving liver function; and reducing liver fat deposition and inflammation.

1.3.1.2 Determination of the HTD1801 ED_{50} in Syrian Golden Hamsters

Syrian golden hamsters (n=10/group) were used to determine the median effective dose (ED_{50}) of HTD1801. The hamsters were fed a high fat diet and treated with 0, 6.25, 12.5, 25, 50, 100, or 200 mg/kg/day HTD1801 respectively. A normal control diet group was included as a normal control. HTD1801 was administered QD for 2-weeks. As expected, HTD1801 treatment resulted in a dose dependent reduction in the elevated serum LDL-C, total cholesterol, and triglyceride levels caused by the high fat diet. The ED_{50} was calculated based the reduction in serum LDL-C levels and was determined to be 45 mg/kg (human equivalent dose [HED] of 425 mg/70 kg).

1.3.1.3 Efficacy Study in Rhesus Macaques with Naturally Occurring Hyperlipidemia/NAFLD

Rhesus macaque is a widely used non-human primate model that closely mimics human physiology in the etiology, pathogenesis, and pathology of hyperlipidemia and NAFLD. The efficacy of HTD1801 was tested in rhesus macaques with naturally occurring hyperlipidemia/NAFLD over a 69-day treatment period. The macaques were fed a diet containing approximately 18% fat and negligible levels of cholesterol. The study consisted of three randomly assigned treatment groups (n=3-4/group): placebo, 15 mg/kg HTD1801 QD (HED of 525 mg/70 kg QD), and 30 mg/kg HTD1801 QD (HED of 1050 mg/ 70kg QD). Treatment with HTD1801 reduced the level of serum LDL-C from baseline in a dose dependent manner. The level of LDL-C in the placebo group remained unchanged throughout the treatment period. Following the washout, serum LDL-C levels increased to pre-treatment levels in the rhesus macaques receiving HTD1801. Similar trends were observed for serum total cholesterol, ALT, and AST levels. HTD1801 treatment also reduced liver fat content in a dose dependent manner, and had a significant blood glucose lowering effect in the rhesus macaques treated with 30 mg/kg HTD1801 compared to the placebo group. These findings suggest that HTD1801 may have beneficial effects on glucose metabolism. There was no effect on body weight or food intake. Notably, HTD1801 was well tolerated in the rhesus macaques throughout the 69-day treatment period.

1.3.1.4 Good Laboratory Practice Toxicity Study in Dogs

The safety and tolerability of HTD1801 was tested in Beagle dogs in a Good Laboratory Practice (GLP) study over a 3-month treatment period. HTD1801 was administered at 60, 200, or 600 mg/kg.

In this study, no mortality occurred and there were no treatment-related effects on clinical chemistry, hematology, and ECG. Repeated oral (capsule) administration of HTD1801 to Beagle dogs, once daily for 91 days was tolerated at a dose of up to 200 mg/kg. The gastrointestinal tract was considered to be the toxicity target, which is consistent with the published adverse effects of BBR or UDCA in clinical practice (see the Section 6.7 in IB). The no-observed adverse effect level (NOAEL) was determined at 60 mg/kg under current study conditions in view of low incidence and/or minimal severity grade of the reversible clinical observations and microscopic changes observed in the 60 mg/kg group. The exposure (mean

C_{max} and mean $AUC_{0\text{-}24h}$) of both BBR and UDCA increased with increasing dose on each testing day, except that the exposure of BBR for the males changed little from 60 to 200 mg/kg on Day 14 and Day 91. No gender differences were observed and no accumulation for UDCA was observed. Accumulation in BBR was noted in some to most animals of each dose. A more detailed summary of the results can be found in the IB.

1.3.2 Clinical Studies in Humans

1.3.2.1 Phase 1 Single Ascending Dose Study – Protocol No. 1801.PCT002

HTD1801 was administered to four cohorts of health male volunteers at dosages of 0.5, 1.0, 2.0, and 4.0 g per day. The results of this trial showed that orally administered HTD1801 is safe and well tolerated in this population at up to 4.0 g per day. Inter-participant variability in PK parameters was generally high across all dose level cohorts. Nevertheless, plasma BBR and unconjugated UDCA levels increased with increasing doses of HTD1801 and dose proportionality was demonstrated for UDCA and BBR $AUC_{(0\text{-last})}$. C_{max} was approximately linear and approaching dose proportionality for UDCA and BBR plasma levels, for HTD1801 dose levels of 1.0-4.0 g. A more detailed summary of these data can be found in the IB.

1.4 Rationale for Treatment and Dose

The dose range for HTD1801 was intended to bracket the intended 1.5 g/day dose for humans, starting with 0.5 g/day, and testing up to 2 g/day or the maximum tolerated dose, whichever is lower. Subjects in the highest dose cohort would receive approximately 0.925 g of BBR and 1.075 g of UDCA. There is interest in carefully investigating the safety of these upper limits which is why the doses to be administered to the highest dose cohort in this study are slightly more than the generally recommended amounts of each compound.

In a previous SAD study, HTD1801 was administered to four cohorts of healthy male volunteers at dosages of 0.5, 1.0, 2.0, and 4.0 g per day. The results of this trial showed that orally administered HTD1801 is safe and well tolerated in health male volunteers at up to 4.0 g per day.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

The primary objective for this study is to assess the safety and tolerability of multiple ascending dose levels of HTD1801 in participants with hypercholesterolemia. Safety assessments will occur throughout the duration of the trial, including monitoring of adverse events (AEs), clinical laboratory tests, vital signs measurements, electrocardiogram, and physical examinations.

2.2 Secondary Objectives

There are four secondary pharmacokinetic (PK)/pharmacodynamic (PD) objectives for this trial.

1. To assess the PK profile of HTD1801 after repeat doses as assessed by derived PK parameters including but not limited to:
   - Plasma half-life of HTD1801 components ($t_{1/2}$)
   - Maximum plasma concentration of HTD1801 components (C_{max})
   - Minimum plasma concentration of HTD1801 components (C_{min})
   - Time to C_{max} (T_{max})
   - Time to C_{min} (T_{min}),
2. To determine the effects of HTD1801 on lipid metabolism:
   - Fasting lipid metabolism and atherogenic biomarkers as assessed by actual values and change from baseline of:
     - Low-density lipoprotein-C (LDL-C)
     - Non-high-density lipoprotein-C (non-HDL-C)
     - Total cholesterol (TC), HDL-C, and TC/HDL-C ratio
     - Apolipoprotein B (ApoB) and A-1 (ApoA1)
     - Triglycerides and free fatty acid (FFA).
     - C- reactive protein (CRP) measured using a high-sensitivity assay
     - Lipoprotein(a) [Lp(a)].
3. To determine the effects of HTD1801 glucose metabolism:
   - Glycosylated hemoglobin (HbA1c) levels.
   - Markers of fasting glucose metabolism as assessed by actual values and change from baseline of:
     - Fasting plasma glucose (FPG).
     - Fasting serum insulin.
     - C-peptide.
4. To determine the effects of HTD1801 on markers of liver function
   - Actual values and change from baseline in ALT and AST.

2.3 Rationale for Study Endpoints

The primary endpoints are related to assessing the safety and tolerability of multiple doses of HTD1801 in overweight to obese hyperlipidemic adults.

The secondary endpoints are related to characterizing the effects of HTD1801 on dyslipidemia in overweight to obese participants. The participant population chosen for this trial allows assessment of both anti-dyslipidemia effects and improvement in insulin sensitivity. Given that the participants enrolled will be overweight to obese, there is expected to be a propensity toward development of T2DM and liver disease (NAFLD/NASH) among the study population. Therefore, the liver function biomarkers AST and ALT, and the glucose metabolism biomarkers FPG, fasting serum insulin, HbA1c and C-peptide will also be evaluated in order to provide insight into the effects of HTD1801 in the study population.

3. STUDY POPULATION

This trial will be performed in overweight to obese participants with hypercholesterinemia.

3.1 Inclusion Criteria

Participants meeting all the following criteria will be eligible to participate in this trial:

1. Have given written informed consent
2. Males or females aged 18 to 70 years old at the time of first dosing
3. Satisfy the following:
   - Females: Non-pregnant and non-lactating; documented surgically sterile, confirmed post-menopausal, or abstinent; or if engaged in sexual relations of childbearing potential, participant agrees to use two acceptable methods of contraception for 4 weeks prior to the treatment period, for the 4 weeks of the Treatment Period, and for at least 2 weeks after the last dose of study drug. One of the methods must be an appropriate hormonal contraceptive (stable for at least 4 weeks prior to treatment), and the other method can be an acceptable method of barrier contraception, e.g., a condom for the male partner.
   - Males: Surgically sterile or abstinent; or if engaged in sexual relations of childbearing potential, the participant and his partner must agree to use an acceptable contraceptive method during the 4 weeks of the Treatment Period and for 2 weeks after the last dose of study drug.
4. Have a body mass index (BMI) of >25.0 and ≤ 45.0 kg/m^2 at Screening
5. Have a documented history of dyslipidemia defined as LDL-C ≥ 2.59 mmol/L.

3.2 Exclusion Criteria

Participants meeting any of the following criteria will be excluded from this trial:

1. The use of any anti-dyslipidemia agent within 28 days prior to dosing
2. History of a total cholesterol ≥ 10.35 mmol/L or triglyceride ≥ 11.3 mmol/L
3. History of a clinically significant cardiac arrhythmia or clinically significant abnormal ECG results at Screening
4. Significant peripheral or coronary vascular disease
5. Clinically significant abnormal blood pressure at Screening, defined as supine blood pressure ≥160/100 or < 90/60 mmHg.
6. Primary hypothyroidism (thyroid stimulating hormone [TSH] > upper limit or normal [ULN] and free T4 < lower limit of normal [LLN]), primary subclinical hypothyroidism (screening TSH > ULN and free T4 within normal limits [WNL]), or secondary hypothyroidism (screening TSH < LLN and free T4< LLN) at Screening.
7. Glucose-6-phosphate dehydrogenase (G6PD) deficiency
8. History of unstable proliferative retinopathy or maculopathy and/or severe neuropathy, in particular autonomic neuropathy, as judged by the Investigator

9. Malignancy within 5 years, except for curatively treated basal cell, squamous cell carcinoma of the skin or carcinoma in-situ of the cervix.
10. Known history of, or positive test for, human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B
11. Active infection that is currently producing symptoms or in which the causative organism of the disease is rapidly reproducing
12. Current or recent history (verbal report) in last 6 months of drug or alcohol abuse, or consumption of more than 30 g of alcohol (3 standard drinks) per day (for male and female participants) within 4 weeks prior to Screening, or positive urine drug screen for drugs of abuse
13. Clinically significant abnormalities identified during physical examination or from the participant's medical history such as:
    a. Any history of cardiac insufficiency defined as New York Heart Association (NYHA) Class II to IV
    b. Angina pectoris within the last 6 months
    c. Acute myocardial infarction at any time
    d. Major surgery within the last 3 months
    e. Stroke
14. Treatment with any agent that decreases body weight, actively enrolled in a weight loss program or following a special diet
15. Gastrointestinal conditions that involve malabsorption or inflammation (e.g., ulcerative colitis, Crohn's disease), and recent or past bariatric surgery of any kind
16. Current or recent use of prohibited medications including (Section 4.4)
17. Current outpatient insulin use, or history of outpatient insulin use for more than 2 weeks in the last year.
18. Whole blood donation or significant blood loss within 30 days prior to screening or Plasma donation within 14 days prior to the first study drug administration.
19. User of any nicotine containing products within the past 6 months.
20. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.
21. Participation in an investigational drug trial within 30 days prior to dosing or 10 half-lives within the last dose of said investigational drug, whichever is longer.
22. The presence of any other conditions, which, in the opinion of the Investigator would make the participant unsuitable for inclusion, or could interfere with the participant participating in or completing the trial.

4. STUDY DESIGN AND PROCEDURES

4.1 Study Design

This is a randomized, double-blind, placebo controlled, multicenter, multiple ascending dose (MAD) study with the primary objective of evaluating the safety and tolerability of HTD1801 in overweight to obese participants with hypercholesterolemia.

There are three planned dose escalation cohorts. Each cohort will consist of 16 participants, randomized 3:1 to receive either HTD1801 or placebo. The three planned cohorts may enroll up to 48 participants. Participants who withdraw from the trial may be replaced following consultation with the Sponsor. The cohorts will be enrolled sequentially. The ascending dose cohort may be initiated once it has been established that HTD1801 is well-tolerated at the previous dose, independent of preliminary efficacy findings.

Participants in each cohort will participate in a Screening Visit, two 2-day in-house visits separated by a 4-week Outpatient Period (includes one Out-Patient Visit), and one Follow-up telephone contact. Eligible participants who are currently taking anti-dyslipidemia medications must consent, with approval of their physician, to discontinue these medications and undergo a Washout Period, prior to completion of screening and participating in the trial. The washout period is at least 4 weeks prior to dosing.

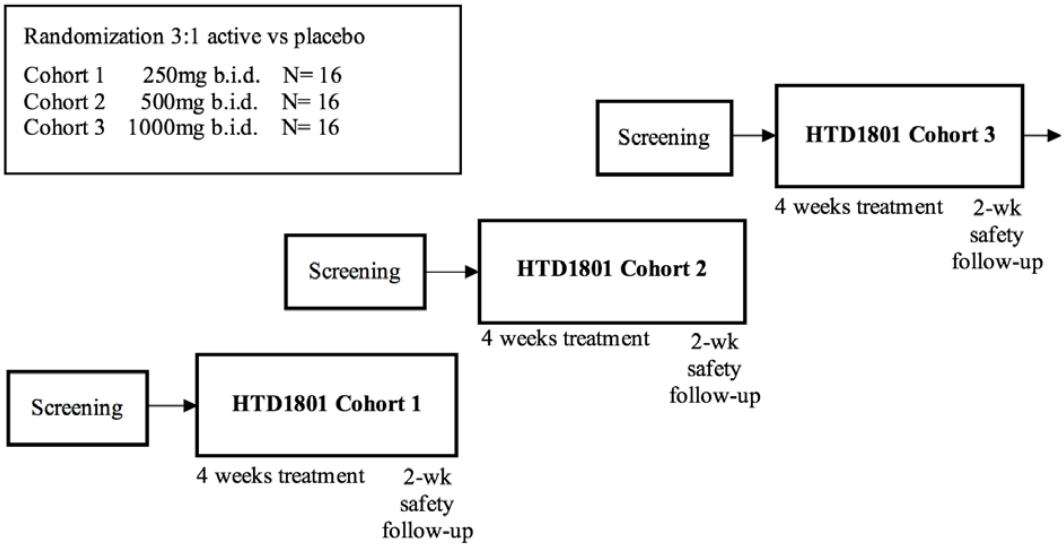
During the first in-house Visit 1, participants will undergo baseline glucose and lipid metabolic assessments on the day prior to dosing, receive their first dose of study drug on Day 1, and undergo post-dosing safety monitoring. On Day 2 the participants will receive their second dose of study medication in the morning, and receive dietary counseling and instruction for taking study drug during the Outpatient Period.

The Outpatient Period will last for approximately 3 weeks. There will be one outpatient visit during this period, on Day 14 (±3 days), to obtain samples for PK, glucose and lipid metabolism biomarkers, liver function biomarkers, vital signs, safety evaluations and to review treatment compliance.

The second in-house Visit 2 will begin on Day 27 (±3 days), followed by discharge on the morning of Day 29 (±3 days). During this period participants will undergo evaluations for PK, glucose and lipid metabolism biomarkers, liver function biomarkers, vital signs, safety evaluations and to review treatment compliance. post-dosing metabolic assessments. A safety Follow-up phone call will occur on Day 42±3. The trial is expected to take approximately ten weeks for each participant from Screening through Follow-up.

Study drug should be administered/taken orally, once per day immediately following the morning meal on Day 1, twice per day following the morning and evening meals on Days 2 to 27 inclusive, and once per day immediately following the morning meal on Day 28. All study drug should be taken with a 240 mL of water (no more). Each in-house visit is expected to last approximately 2 days.

Figure 4-1 Overall Study Design Schematic



4.2 Study Procedures

See Table 1 for the Schedule of Time and Events which summarizes the tests and evaluations to be performed on each study day.

4.2.1 Screening Period

The Screening Period will generally begin approximately 28 days before the first dose of study drug. Written informed consent must be obtained prior to the initiation of any study-related procedures. Investigators must account for all participants who sign informed consent forms. The Investigator or designee will keep a Participant Screening and Enrollment Log at the investigational site.

All inclusion and exclusion criteria must be met during the Screening Period. These screening procedures will include the collection of demographic information, and a thorough medical history. Potential participants will undergo a physical examination including height and weight, the collection of vital signs (blood pressure, heart rate, respiratory rate, temperature measured after at least 5 minutes in a seated position), 12-lead ECG, a urine drug screen and an alcohol breath test. Females of child-bearing potential will qualify based on a urine pregnancy test (to be confirmed prior to Baseline by a serum pregnancy test). Potential participants will also provide a fasting urine sample for urinalysis, and fasting blood samples for hematology, clinical chemistry, lipids, HIV, hepatitis B and C, G6PD, TSH, and Free T4.

Eligible participants who are currently taking anti-dyslipidemia agents will need to discontinue those agents for at least 28 days prior to Baseline measurements. Inclusion and Exclusion criteria (excluding the confirmatory serum pregnancy test result) must be met prior to the washout of anti-dyslipidemia medications. Participants will be educated about the factors that may influence insulin sensitivity or lipid metabolism, such as strenuous exercise, alcohol, certain medications, dietary supplements, caffeine, smoking and illness/infection.

Participants who have failed screening may be allowed to re-screen once at the discretion of the Investigator. A new screening number will be assigned.

4.2.2 Visit 1 (Baseline and Dosing)

Participants will be asked to report to the clinic in a fasting state, and to undergo the following:

- Urine drug screen and an alcohol breath test
- Serum pregnancy test (for females of child-bearing potential)
- Weight (baseline) and vital signs (baseline is pre-dose, then one hour post-dose, and pre-discharge on Day 2),
- Baseline information to update medical history and current medications,
- Baseline blood sampling for:
    - PK (-18 hr, -12 hr, -6 hr and pre-dose),
    - hematology,
    - clinical chemistry,
    - lipids,
    - liver function biomarkers AST and ALT, if not included in standard panel above,
    - glucose metabolism biomarkers (HbA1c, FPG, fasting insulin, and fasting C-peptide), if not included in standard panel above,
    - C-reactive protein (high-sensitivity), if not included in panels above,
    - FFA, ApoA1, ApoB, Lp(a) and LDH, if not included in one of the panels above.
- Urinalysis
- Baseline ECG

The procedures outlined above can occur at any time during the pre-dose period once the participant has arrived at the study site, except as noted for blood PK sampling which should occur prior to a standardized morning meal on what will be referred to as the beginning of Day 1.

Immediately following the morning meal, the participant will then receive their first dose of study drug, under supervision. The dose is to be taken with 240 mL of water (not more). Post-dose PK sampling will begin as described in Table 2. A 12-lead ECG is to be performed approximately 3 hrs post-dose.

Any adverse changes from Baseline represent an adverse event.

Participants will begin twice per day dosing on the morning of Day 2. The morning dose on Day 2 will be administered under the supervision of qualified study personnel. Participants will receive dietary counseling on Day 2 in preparation for the Outpatient Period. Participants will be discharged on Day 2 after the morning 24-hr PK sample, after which they will self-administer the study drug at home. Participants will be instructed to return to the study site in a fasted state and with their supply of study drug on Day 14±3.

4.2.3 Outpatient Period (with one Outpatient Visit)

Participants are to continue taking the study drug twice daily throughout the Outpatient Period, after breakfast and after dinner. The amount of liquid is not restricted.

Upon their return to the study site on Day 14±3 in a fasted state and with their supply of study drug, participants will undergo the following:

- Urine drug screen and an alcohol breath test
- Physical examination including weight and vital signs,
- Update current medications (new medications raise the possibility of being needed to treat an adverse event),
- Urine pregnancy test for women of child-bearing potential,
- Blood sampling for:
    - hematology,
    - clinical chemistry,
    - lipids,
    - liver function biomarkers AST and ALT, if not included in standard panel above,
    - glucose metabolism biomarkers (HbA1c, FPG, fasting insulin, and fasting C-peptide), if not included in standard panel above,
    - C-reactive protein (high-sensitivity), if not included in panels above,
    - FFA, ApoA1, ApoB, Lp(a) and LDH, if not included in one of the panels above.
- Urinalysis
- ECG

- Study drug compliance check

Adverse changes from Baseline represent an adverse event.

Participants will again be counseled about proper dietary habits and be discharged from the study site, with instructions to return to the study site with their supply of study drug on Day 27±3. Fasting is not required for arrival on Visit 2.

4.2.4 Visit 2 (Final Assessments)

Participants are to return to the clinic on Study Day 27±3. The morning dose of study drug will have been taken at home. Participants will be asked to undergo the following:

- Urine drug screen and an alcohol breath test
- Physical examination including weight and vital signs,
- Update current medications (new medications raise the possibility of being needed to treat an adverse event),
- Urine pregnancy test for women of child-bearing potential,
- ECG
- Study drug compliance check

The following day (Day 28±3), participants are to undergo the following in a fasted state:

- Vital signs
- Blood sampling for:
  - hematology,
  - clinical chemistry,
  - lipids,
  - liver function biomarkers AST and ALT, if not included in standard panel above,
  - glucose metabolism biomarkers (HbA1c, FPG, fasting insulin, and fasting C-peptide), if not included in standard panel above,
  - C-reactive protein (high-sensitivity), if not included in panels above,
  - FFA, ApoA1, ApoB, Lp(a) and LDH, if not included in one of the panels above.
- Urinalysis

Following the completion of these sample collections, a standardized morning meal is to be given to the participants. The participant will then receive their final dose of study drug, under

supervision, and post-dose PK sampling will begin as described in Table 2. A 12-lead ECG is to be performed approximately 3 hrs post-dose.

Participants will be discharged on the morning of Day 29±3 following the 24 hr post-dose PK blood sample, collection of vital signs, and AE evaluation, assuming they are considered by the investigator to be stable and suitable for discharge. Participants will be advised to expect and be ready for a follow-up phone call from the study site approximately 2 weeks later.

4.2.5 Follow-up

A safety follow-up call will be performed by study site personnel on Day 42±3. At that time, the participants will be asked about their general health and be queried for any findings that might be considered an adverse event. Following that call, and assuming there are no adverse conditions that require follow-up, participants will be terminated form the study.

4.3 Dose Escalation, Study Discontinuation and Stopping Criteria

4.3.1 Dose Escalation Algorithm

This trial includes three planned dose escalation cohorts. The doses of HTD1801 to be administered are summarized below in Table 4.

Table 4. Planned Dose Escalation Cohorts

Cohort Number	Number of Participants Planned	Dose Regimen
1	12	HTD1801: 500 mg/day (250 mg bid)
	4	Placebo: 2 tablets/day (1 tablet bid)
2	12	HTD1801: 1000 mg/day (500 mg bid)
	4	Placebo: 4 tablets/day (2 tablets bid)
3	12	HTD1801: 2000 mg/day (1000 mg bid)
	4	Placebo: 8 tablets/day (4 tablets bid)

4.3.2 Dose Escalation Stopping Criteria

Participants will stop the study drug if any of the following stopping rules are met:

- Clear toxicity of the study medication or any anaphylaxis.
- Increase in LDL-C more than 3-times compared to baseline.
- Decrease in HDL-C to less than 33% of baseline result.
- ALT or AST increase 3-times above the reference range.
- Profuse diarrhea, gastroparesis or vomiting.
- Signs and symptoms of hepatitis.

- Two (2) or more of the participants in a cohort experience severe AEs, judged to be at least possibly study drug related by the Investigator
- Fifty percent (50%) or more of the participants experience moderate to severe AEs, judged to be at least possibly study drug related by the Investigator
- Two (2) or more participants develop similar clinically significant laboratory, ECG, or vital sign abnormalities, or severe AEs in the same organ class, indicating dose-limiting intolerance. Dose escalation could proceed if, after review of the data by the Investigator and discussion with Sponsor, it was concluded that the events were not drug related.

4.3.3 Criteria for Early Termination of the Study

The trial will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- New information or other evaluation regarding the safety or efficacy of the trial medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the trial.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.
- Failure to meet expected enrollment goals.
- Administrative reasons.

The Sponsor, Human Research Ethics Committee (HREC), or regulatory authority may elect to terminate or suspend the trial or the participation of an investigational site at any time.

4.3.4 Criteria for Early Termination of Individual Participants

Participants may withdraw their consent to participate in the trial at any time.

If a participant withdraws consent, the date and reason for consent withdrawal should be documented. Participants will be encouraged to remain in the clinic for safety assessments until the Investigator deems that it is safe for the participant to be discharged. Participant data will be included in the analysis up to the date of the consent withdrawal.

- An AE that requires discontinuation at the discretion of the Investigator.
- Lost to follow-up. The participant did not return to the clinic and attempts to contact the participant were unsuccessful. Attempts to contact the participant must be documented.
- Voluntary withdrawal of consent (mandatory removal from trial).
- Discretion of Investigator (document reason on the case report form [CRF]).
- Participant becomes pregnant or begins breastfeeding (mandatory).

Wherever possible, the tests and evaluations, including those listed for the Follow-up Visit should be performed for all participants who discontinue prior to the completion of the trial.

In the event the Investigator terminates a participant's participation in the study, the Investigator must notify the Sponsor of such decision and rationale immediately in writing. In all cases, the appropriate HREC and other applicable regulatory authorities shall be informed.

4.4 Prohibited Medications

Use of the agents listed in Table 5. (prescription or nonprescription) is prohibited from the time points specified until completion of all trial activities.

Table 5. Prohibited Medications

Medication or Class	Indication	Reason	From time point specified
Oral anti-diabetic medication other than metformin (sulfonylurea, dipeptidyl peptidase-4 inhibitor or acarbose).	Glycemic control	Affect glucose metabolism	Within 12 weeks prior to dosing.
Thiazolidinedione		Affect glucose metabolism	Within 12 weeks prior to dosing.
Glucagon-like-peptide-1 analogues		Affect glucose metabolism	Within 12 weeks prior to dosing.
Omega-3 fatty acids, and nicotinic acid or derivatives of nicotinic acid	Atherogenic plaque and prevention of atherogenesis	Affect lipid metabolism and bioavailability	Must be stable at least 12 weeks prior to dosing.
Systemic corticosteroids.	Inflammation	Affect carbohydrate and lipid metabolism	Within 6 weeks prior to dosing.
Fibrates	Dyslipidemia	Affect lipid bioavailability and distribution	Within 4 weeks prior to dosing.
Antihypertensives	Hypertension	Safety- uncontrolled hypertension can increase number of AE or SAE.	Must be stable at least 4 weeks prior to dosing.

4.5 Contraception

Female participants must be non-pregnant and non-lactating, and either surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal, abstinent, or if engaged in sexual relations of childbearing potential, must be willing to:

1. Use one of the following contraceptive methods for 4 weeks prior to the treatment period, for the 4 weeks of the Treatment Period, and for at least 2 weeks after the last dose of study drug (total of 10 weeks):
    a. Abstinence from heterosexual intercourse OR

b. Use a highly-effective form of contraception (e.g. hormonal contraception, or an intrauterine device)

AND

2. Use a barrier method (by the female or her sexual partner).

The adequacy of other methods of contraception will be assessed on a case-by-case basis by the Principal Investigator (PI).

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

The site will make an effort to retrieve medical records to document sterility. Postmenopausal status will be confirmed through testing of FSH levels ≥ 40 IU/mL at screening for amenorrheic female participants <55 years of age

A urine pregnancy test will be performed for female participants at Screening, at the Check-in visits for the in-house periods, Day 14, and Day 27. Serum pregnancy test will be conducted when urine pregnancy test is positive at screening.

Male participants must be surgically sterile, abstinent, or if engaged in sexual relations of child-bearing potential, the participant and his partner must be using the contraceptive methods described above for the 4 weeks of the Treatment Period, and for at least 2 weeks after the last dose of study drug.

Male participants will be advised not to donate sperm during this period.

4.6 Dietary Counseling

Participants will be counseled to follow the healthy eating practices at the time points indicated in the SOE.

At each period, the importance of maintaining the body weight within a 5% range throughout the study will be explained. The counseling for each participant will be individualized based on their actual measured body weight. Additionally, participants will be counseled to maintain their normal diet and exercise regimen. They will be instructed not to start any new diets, supplements, or exercise programs during the study, and to avoid overeating and high sodium and salt intake on the day before check-in.

Instructions are based on the US Department of Agriculture' 2015-2020 key recommendations that recommend a healthy eating pattern that accounts for all foods and beverages within an appropriate calorie level.

A healthy eating pattern includes:

- A variety of vegetables from all of the subgroups-dark green, red and orange, legumes (beans and peas), starchy, and other

- Fruits, especially whole fruits
- Grains, at least half of which are whole grains
- Fat-free or low-fat dairy, including milk, yogurt, cheese, and/or fortified soy beverages
- A variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), and nuts, seeds, and soy products
- Oils

A healthy eating pattern limits:

- Saturated fats and trans fats, added sugars, and sodium

Key Recommendations that are quantitative are provided for several components of the diet that should be limited. These components are of particular public health concern in the United States, and the specified limits can help individuals achieve healthy eating patterns within calorie limits:

- Consume less than 10 percent of calories per day from added sugars
- Consume less than 10 percent of calories per day from saturated fats
- Consume less than 2,300 milligrams (mg) per day of sodium

If alcohol is consumed, it should be consumed in moderation—up to one standard drink per day for women and up to two standard drinks per day for men.

5. STUDY MATERIALS

5.1 Investigational Products

5.1.1 HTD1801

Study drug will be provided by the Sponsor in the form of film-coated tablets suitable for oral administration, with each tablet containing either 250 mg of HTD1801 or placebo. The study drug should be taken with 240 mL of water. There are no particular post-dose fasting requirements or water restrictions.

5.1.2 Placebo

The placebo is identical in appearance to the active HTD1801. Within each cohort the number of tablets of placebo will be the same as the number of tablets of active study drug.

5.2 Packaging, and Labeling of Investigational Products

The Sponsor will provide the Investigator with the labeled study drug in accordance with specific country regulatory requirements. When a participant is enrolled, a pre-randomized kit will be dispensed to the participant.

5.3 Storage and Drug Accountability of Investigational Products

All study drug should be stored in a monitored 2-8^{o}C refrigerator in the original containers. Containers should be kept tightly closed and should not be exposed to moisture, excessive heat or direct sunlight.

The study staff are required to document the receipt, dispensing, and return/destruction of study drugs and supplies provided by or on behalf of the Sponsor. At the end of the trial, the study site must return all unused study drug and unopened containers to the Sponsor or designee, or destroy them upon request. The study drug supplies will be counted and reconciled at the site before being returned to the Sponsor or designee, or being destroyed.

Investigational product taken home for the outpatient period should be stored in a refrigerator. The participants do not have to maintain refrigeration during daily transportation or for the duration of a day or weekend trip, provided the drug product is kept away from sources of excessive heat (e.g., not left out in the sun or in a non-air-conditioned vehicle, etc.).

No study drugs may be dispensed to any person not enrolled in the trial.

Treatment compliance will be monitored using standard methods including but not limited to: drug PK measurements, drug accountability assessments (i.e., pill counting), and any other methods deemed appropriate for this trial.

6. ADVERSE EVENTS

6.1 Definitions

6.1.1 Adverse Event

An AE is any undesirable and unintended medical event occurring to a participant in a clinical trial, whether or not related to the study products. This includes events from the first study related activity after the participant has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following should not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first study related activity after the participant has signed the informed consent.
- Pre-existing conditions found as a result of screening procedures.
- Pre-existing events that have not worsened in intensity or frequency from baseline.

6.1.2 Treatment Emergent Adverse Event

A treatment-emergent AE (TEAE) is defined as any clinically significant event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

6.1.3 Clinical Laboratory Event

A clinical laboratory AE is any clinically significant laboratory abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e. change of dose, discontinuation of investigational study product, more frequent follow-up or diagnostic investigation).

A laboratory re-test and/or continued monitoring of an abnormal value is not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

6.1.4 Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that at any dose

- Results in death
- Is life threatening. The term “life threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE.

- Results in persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Is an important medical event that satisfies any of the following:
  - May require intervention to prevent items 1 through 5 above.
  - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

6.1.5 Severity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient, easily tolerated by the participant and does not affect the participant's daily activities.
Moderate:	The event causes the participant discomfort and interrupts the participant's usual daily activities.
Severe:	The event is incapacitating and causes considerable interference with the participant's usual activities.

6.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Not related:	The event is clearly related to other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the IP.
Unlikely:	The event was most likely produced by other factors such as the participant's clinical state, therapeutic interventions, or a concomitant drug administered to the participant and does not follow a known response to the IP, although a causal relationship cannot be ruled out.
Possible:	The event follows a reasonable temporal sequence from the time of IP administration or follows a known response to the IP but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
Probable:	The event follows a reasonable temporal sequence from the time of IP administration and follows a known response to the IP and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.

6.2 Recording and Reporting Procedures

6.2.1 Collection and Recording of AEs

Collection of all AEs (serious and non-serious) will commence from the time the participant signs the informed consent to participate in the study. At each study visit or Study Day, the Investigator or designee will assess whether any AEs have occurred. In order to avoid bias in eliciting adverse events, a non-specific question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study.

All participants experiencing AEs, whether considered associated with the use of the study medication or not, should generally be monitored until the symptoms subside, any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE eCRF, whether or not the Investigator concludes that the event is related to the drug treatment. The event term, start and stop dates and severity, action taken with study drug, outcome, will be documented, along with the Investigator's opinion of the causal relationship between the event and the study drug.

6.2.2 Collection and Reporting of SAEs

The Sponsor has a legal responsibility to notify the appropriate regulatory authorities about the safety of the IMP. Accordingly, the Investigator must report all SAEs, regardless of presumed causal relationship, to the sponsor's assigned safety representative (INC Research Safety & Pharmacovigilance), by fax or email on a SAE Form within 24 hours of learning of the event. INC Research Safety & Pharmacovigilance will forward the information to the Sponsor with preliminary review and assessment comments.

INC Research Safety & Pharmacovigilance fax/email details:

Attention: INC Research Safety & Pharmacovigilance

Local Toll-Free Fax (Australia): 1800 256 952
Alternate (Global) Fax: +1 877 464 7787
Email: INCDrugSafety@incresearch.com
For medical emergencies contact:
Dr. David Fuller (Medical Monitor), phone: +61 (0) 450 965 709

Information on SAEs will be recorded on a SAE Form. Blank copies are included in the study Investigator's File. It is not acceptable for the Investigator to send photocopies of the subjects' medical records to INC Research Safety & Pharmacovigilance in lieu of completion of the appropriate AE CRF page and / SAE Form. However, there may be instances when copies of medical records for certain cases are requested by INC Research Safety & Pharmacovigilance. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission.

The completed SAE Form and SAE Fax Cover Sheet should be sent via fax or email immediately upon completion to the Sponsor's assigned safety representative (INC Research Safety & Pharmacovigilance). Additional relevant information or clinical follow-up should be sent via fax or email to the Sponsor through INC Research Safety & Pharmacovigilance as soon as it becomes available. The Investigator should follow up the event until resolution or stabilization of the condition. Follow-up reports (as many as required) should be completed and faxed following the same procedure above.

A final report is required in any case once the condition is resolved or stabilized and no more information about the event is expected. The final report should be completed and faxed or emailed following the same procedure above.

All pregnancies in a female subject or in a female partner of a male study subject should be reported on a Pregnancy Report Form following the same reporting process and timelines required for SAEs.

The Investigator must keep a copy of all documentation related to the event in the site's study files.

If the Investigator learns of any SAE, including death, at any time after a subject completes the study, and he/she considers the event reasonably related to the IMP, the Investigator will promptly notify the Sponsor (through INC Research Safety & Pharmacovigilance) and the Medical Monitor. This shall include pregnancy in a female subject or in a female partner of a male study subject.

When an SAE occurs, it should be reported according to the following procedure:

An SAE form must be completed immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum a short description of the event and the reason why the event is categorized as serious, participant identification number, Investigator's name, name of the study medication and a causality assessment.

The collection of SAEs will begin after the participant signs the informed consent form and will stop at the end of the participant's follow-up period.

6.3 Anticipated Adverse Events

Anticipated adverse events are primarily gastrointestinal in nature, and mild-to-moderate in severity.

6.4 Follow-up of Adverse Events and Serious Adverse Events

All adverse events should be followed until resolution, or until the Investigator and Sponsor conclude that further follow-up is not necessary.

If information on SAEs is not available at the time of the first report and becomes available at a later date, the Investigator should provide that information to the Sponsor within 24 hours of receipt of the information. Copies of any relevant data from the hospital notes, which may or

may not include ECGs, laboratory tests, discharge summary and/or postmortem results, should be sent accordingly. The Sponsor or designated qualified vendor will be responsible for all reporting to regulatory authorities.

6.5 Safety Monitoring Committee

The Safety Monitoring Committee (SMC) is expected to consist of

- the Principal Investigator (PI) at each site,
- an independent local INC Medical Monitor,
- others as may be requested by the Principal Investigator.

The members of SMC will review the safety data before the decision is made to advance to the next dose cohort.

7. DATA HANDLING AND MANAGEMENT

7.1 Data Management

The full details of procedures for data handling will be documented in the Data Management Plan (DMP).

AEs and medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (DDE). The MedDRA version used will be recorded in the Study Master File documentation.

Unique numbers will identify the participant and the biological material obtained from the participant. Appropriate measures such as encryption or deletion will be enforced to protect the identity of human participants in all presentations and publications as required by local/regional/national requirements.

Data from screening failures will not be entered into the database.

Laboratory data from the central laboratory will be electronically transferred to INC Research for database reconciliation purposes. The electronic laboratory data will be considered source data. In cases where sensitive non-PK laboratory data is transferred via non-secure electronic networks, data will be encrypted during transfer.

All other results, including PK, PD data, and laboratory tests will be transferred electronically to the responsible Data Management Unit.

7.2 CRFs (Electronic)

7.2.1 Clinical Data Management Workflow

*e*CRFs will be developed by appropriate personnel, in collaboration with the clinical trial team and statistician. Those responsible for data management will document the process workflow in the Data Management Plan (DMP). After data entry, monitor(s) will source data verify (SDV) the *e*CRFs against the source documents. Queries may be issued to clarify the data entered. The PI will electronically sign the *e*CRFs after all data have been entered and all queries have been resolved. If corrections and/or resolution of queries are required after Investigator approvals, those *e*CRFs affected by changes will be re-signed by the PI. The database may be locked after the PI approvals are completed.

The Investigator will receive all laboratory data electronically or based on FAX reports directly from the laboratory. An Investigator must review, evaluate, sign, and date the laboratory reports upon receipt.

After database lock, CDM study design documentation and locked *e*CRFs (PDF) will be created and will be provided to the Sponsor, if requested.

7.2.2 Data Entry of Electronic Case Report Forms

Data required for analyses and participant safety assessments will be entered from source documentation into *e*CRFs. Instructions for data entry will be provided in the *e*CRF Completion Guidelines, developed by the local sponsor's Data Management Department. All site staff involved with entering data into the *e*CRFs will be trained prior to gaining access to the study database.

7.2.3 Corrections to Electronic Case Report Forms

Queries may be generated by the *e*CRF system during data entry, and queries may be generated by data management personnel, staff, monitors, PIs, the Sponsor, and other data reviewers during the course of the study. Only specific site personnel will be authorized to make corrections to the *e*CRFs with the permission of the Investigator. Corrections will be made directly in the *e*CRF – by modifying existing data, adding new data, or deleting data, as appropriate. All data corrections will be logged in the electronic audit trail.

7.2.4 Investigator Approval of Electronic Case Report Form Data

The Investigator or Investigator's authorized staff must ensure that all information derived from source documentation is consistent with the source information and accurately reflected in the *e*CRFs. By electronically signing the *e*CRFs, the Investigator confirms that the information is complete and correct.

7.3 Retention of Documents

Participant notes must be kept for the maximum period permitted by the hospital, institution, or private practice. Other source documents and the Investigator's Trial File must be retained for at least 15 years or longer in accordance with local regulation.

The Investigator must agree to archive the documentation pertaining to the trial in an archive after completion or discontinuation of the trial if not otherwise notified. The Investigator should not destroy any documents without prior permission from the Sponsor.

8. STATISTICAL METHODS

8.1 Statistical and Analytical Plans

The data will be summarized in tables by treatment group, as appropriate, showing the number of subjects with nonmissing data (n), mean, standard deviation, median, minimum, and maximum for continuous data and showing counts and percentage for categorical data. Data will also be listed as deemed appropriate.

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

8.2 Sample Size Calculation

For the current study, the sample size for the safety evaluation was determined based on experience from typical initial clinical safety studies. Sufficient number of participants will be enrolled to assess safety at a given dose level such that decisions can be made to escalate to the next dose level. This study is not intended to show statistical differences of treatment effects between groups.

8.3 Analysis Population

The following populations will be used to summarize and analyze the study data.

- Safety Population: Includes all participants who received at least one dose of study drug or placebo.
- Efficacy Population: Includes all participants who received at least one dose of study drug or placebo, and had at least one post-dose assessment for the various secondary endpoints.
- PK Population: Includes all participants who received active drug (HTD1801) and have sufficient data to calculate the PK parameters for UDCA and/or BBR.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Monitoring

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol and GCP are followed, CRFs are completed correctly, and drug accountability is monitored. The Monitor will visit the study site at least once before First Participant First Visit (FPFV) (Initiation Visit), at least once during the clinical part of the study, and at least once after Last Participant Last Visit (LPLV). Furthermore, the Monitor must be available for discussions by telephone.

The Monitor must be given direct access to source documents, such as original documents, data, and records. Direct access includes permission to examine, analyze, verify and reproduce any record(s) and report(s) that are important to evaluation of the clinical trial. The study will be monitored to verify integrity and validity of the data. Monitoring will follow a Monitoring Plan.

9.2 Protocol Deviations

The Investigator must not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other circumstances arise that will require deviation from protocol-specified procedures, the Investigator is directed to contact the Sponsor in advance to review and discuss the implications of the deviation and determine the appropriate course of action. The Investigator is not otherwise authorized to deviate from the protocol without Sponsor permission, and with notification sent to the HREC. Any deviation must be documented, stating the reason and date, the action taken, and the impact for the participant and/or the study. The documentation must be kept in the Investigator's Study File and the Sponsor's Study Master File.

10. ETHICAL ASPECTS OF THE STUDY

This study will be conducted in accordance with the principles that have their origin in the Declaration of Helsinki (World Medical Association), the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) Guidance E6, and all other applicable regulatory requirements.

10.1 Institutional Review Board and/or Independent Ethics Committee

Prior to commencement of the study, the protocol, any amendments, participant information/informed consent form, any other written information to be provided to the participant, participant recruitment procedures, information about payments and compensation available to participants if not mentioned in the participant information, the Investigator's current curriculum vitae (CV) and/or other documentation evidencing qualifications, and other documents as required by the local HREC should be submitted. Written approval/favorable opinion must be obtained from HREC prior to commencement of the clinical trial.

During the trial, the Investigator must promptly report the following to the HREC: Updates to the Investigator's Brochure (IB), unexpected SAEs where a causal relationship cannot be ruled out, substantial amendments to the protocol, non-substantial amendments, deviations to the protocol implemented to eliminate immediate hazards to the participants, new information that may affect adversely the safety of the participants or the conduct of the study (including new risk/benefit analysis in case it will have an impact on the planned follow-up of the participants), annually written summaries of the study status and other documents as required by the local HREC.

Substantial amendments must not be implemented before approval, unless necessary to eliminate hazards to the participants.

The Investigator must maintain an accurate and complete record of all submissions made to the HREC. The records should be filed in the Investigator's Trial File and copies must be provided to the Sponsor.

10.2 Informed Consent

Once signed, the original informed consent form, participant authorization form (if applicable), and participant information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed informed consent form, the signed participant authorization form (if applicable), and participant information sheet (if applicable) shall be given to the participant.

All revised informed consent forms must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised informed consent form.

10.3 Participant Confidentiality

The Sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age, or date of birth, and participant initials may be used to verify the participant and accuracy of the participant's unique identification number.

The Investigator must agree to permit the Sponsor's monitor or designee's monitor, representatives from any regulatory authority, the Sponsor's designated auditors, and the HREC to review the participant's source data or documents, including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process. Copies of any participant source documents that are provided to the Sponsor must have certain personally identifiable information removed.

11. PUBLICATION, DISCLOSURE, AND CLINICAL TRIAL REGISTRATION POLICY

The Investigator will provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

All publications and presentations must be prepared in accordance with this section and the Master Services Agreement or equivalent agreement. In the event of any discrepancy between the protocol and the Master Services Agreement or equivalent agreement the Master Services Agreement or equivalent agreement will prevail.

12. REFERENCES

Dong et al. 2013
Dong H, Zhao Y, Zhao L, Lu F. (2013). The Effects of Berberine on Blood Lipids: A Systemic Review and Meta-analysis of Randomized Controlled Trials. *Planta Med.* 79(6):437-46. Doi:10.1055/s-0032-1328321.

Lan et al. 2015
Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, Sun G. (2015). Meta-Analysis of the Effect and Safety of Berberine in the Treatment of Type 2 Diabetes Mellitus, Hyperlipidemia, and Hypertension. *J. Ethnopharmacol.* 161:69-81. doi:10.1016/j.jep.2014.09.049.

Mitchell et al. 2016
Mitchell S, Roso S, Samuel M, Pladevall-Vila M. Unmet Need in the Hyperlipidemia Population with High Risk of Cardiovascular Disease: A Targeted Literature Review of Observational Studies. *BMC Cardiovasc Disord.* 16:74. doi:10.1186/s12872-016-0241-3.

NCEP 2002
National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institute of Health (2002). *Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. (Report No. 02-5215). Retrieved from: http://circ.ahajournals.org/content/106/25/3143

Nelson 2013
Nelson RH. (2013). Hyperlipidemia as a Risk Factor for Cardiovascular Disease. *Prim Care.* 40(1):1995-211. doi:10.1016/j.pop.2012.11.003.

Rosei and Salvetti 2016
Rosei EA and Slavetti M. (2016). Management of Hypercholesterolemia, Appropriateness of Therapeutic Approaches and New Drugs in Patients with High Cardiovascular Risk. *High Blood Press Cardiovasc Prev.* 23(3):217-230. doi: 10.1007/s4029*2-016-0155-2.

Singh and Mahajan 2013
Singh IP and Mahajan S. (2013). Berberine and its Derivatives: A Patent Review (2009-2012). *Expert Opin Ther Pat.* 23(2):215-31. doi: 10.1517/13543776.2013.746314.

Tavori et al. 2016
Tavori H, Giunzioni I, and Fazio S. (2016). PCSK9 Inhibition to Reduce Cardiovascular Disease Risk: Recent Findings from the Biology of PCSK9. *Curr Opin Endocrinol Diabetes Obes.* 22(2):126-132. doi: 10.1097/MED.0000000000000137.

Zhu et al. 2015
Zhu GQ, Shi KQ, Huang S, Huang GQ, Lin YQ, Zhou ZR, Braddock M, Chen YP, Zheng MH. (2015). Network Meta-Analysis of Randomized Controlled Trials: Efficacy and Safety of UDCA-Based Therapies in Primary Biliary Cirrhosis. *Medicine (Baltimore)*. 94(11):e609. doi:10.1097/MD.0000000000000609.

13. APPENDICES

13.1 Principal Investigator Compliance Statements

Principal Investigator Compliance Statement

The Principal Investigator agrees to conduct the trial as outlined in this protocol with reference to international/national/local regulations and in accordance with current Good Clinical Practice (GCP) guidelines, and the current version of the Declaration of Helsinki. Any modification to the protocol must be agreed upon in advance by both the Investigator and HighTide Biopharma Pty. Ltd., and documented in writing. By written agreement to this protocol, the Investigator approves of the protocol and agrees to allow direct access to all documentation, including source data, to authorized individuals representing HighTide Biopharma Pty. Ltd., (including monitoring staff and auditors), to Human Research Ethics Committees (HREC), and/or to regulatory authorities.

Name:
Title: Principal Investigator
Facility/Institution:

Telephone:
Fax:
E-mail:

Signature: _____ Date: _____