CLINICAL STUDY PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase 2, Dose-Finding Study to Evaluate the Efficacy and Safety of LIB003 in Patients on Stable Lipid-Lowering Therapy Requiring Additional LDL-C Reduction

Investigational Product: LIB003
Protocol Number: LIB003-002
IND Number: 134579

Sponsor:
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Confidentiality Statement

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SIGNATURE PAGE

STUDY TITLE: Randomized, Double-Blind, Placebo-Controlled, Phase 2, Dose-Finding Study to Evaluate the Efficacy and Safety of LIB003 in Patients on Stable Lipid-Lowering Therapy Requiring Additional LDL-C Reduction

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
_____	_____

Evan A. Stein, MD PhD
Chief Medical Officer
LIB Therapeutics, LLC

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by LIB Therapeutics to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to LIB Therapeutics and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by LIB Therapeutics, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethic Committee Regulations, and ICH Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: Randomized, Double-Blind, Placebo-Controlled, Phase 2, Dose-Finding Study to Evaluate the Efficacy and Safety of LIB003 in Patients on Stable Lipid-Lowering Therapy Requiring Additional LDL-C Reduction

PROTOCOL NUMBER: LIB003-002

INVESTIGATIONAL PRODUCT: LIB003

PHASE: 2

INDICATION(S): Low-density lipoprotein cholesterol (LDL-C) reduction in patients with atherosclerotic cardiovascular disease (ASCVD), high risk of ASCVD, or heterozygous familial hypercholesterolemia (HeFH) who need additional LDL-C reduction

OBJECTIVES:

The co-primary objectives of this study are to assess the percent change from baseline in LDL-C level as the mean of weeks 10 and 12 and at week 12 (both calculated by Friedewald formula) with monthly (Q4W) dosing of various doses of LIB003 administered subcutaneously (SC) in patients with hypercholesterolemia on stable diet and oral LDL-C-lowering drug therapy. The secondary objectives of this study are the following:

- To re-assess the LDL-C lowering effects of the primary objectives with LDL-C calculated by Hopkins formula or preparative ultracentrifugation;
- To assess safety and tolerability of various multiple doses of LIB003;
- To assess the pharmacodynamic (PD) effects of various multiple doses of LIB003 on plasma unbound (free) proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations;
- To assess the effects of LIB003 on serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non–HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TG);
- To assess the effects of LIB003 on apolipoprotein (apo) B, apo A1, and lipoprotein (a) (Lp[a]) serum concentrations;
- To assess the PK of LIB003 and PCSK9 following various multiple doses of LIB003; and
- To assess the frequency of anti-drug (anti-LIB003) antibodies (immunogenicity) following multiple SC doses of LIB003.

The exploratory objectives of this study are the following:

- To assess the effect on LDL-C and free PCSK9 6 and 8 weeks after the last dose of LIB003, and
- To assess the effects on other lipid and cardiovascular risk biomarkers as appropriate.

POPULATION:

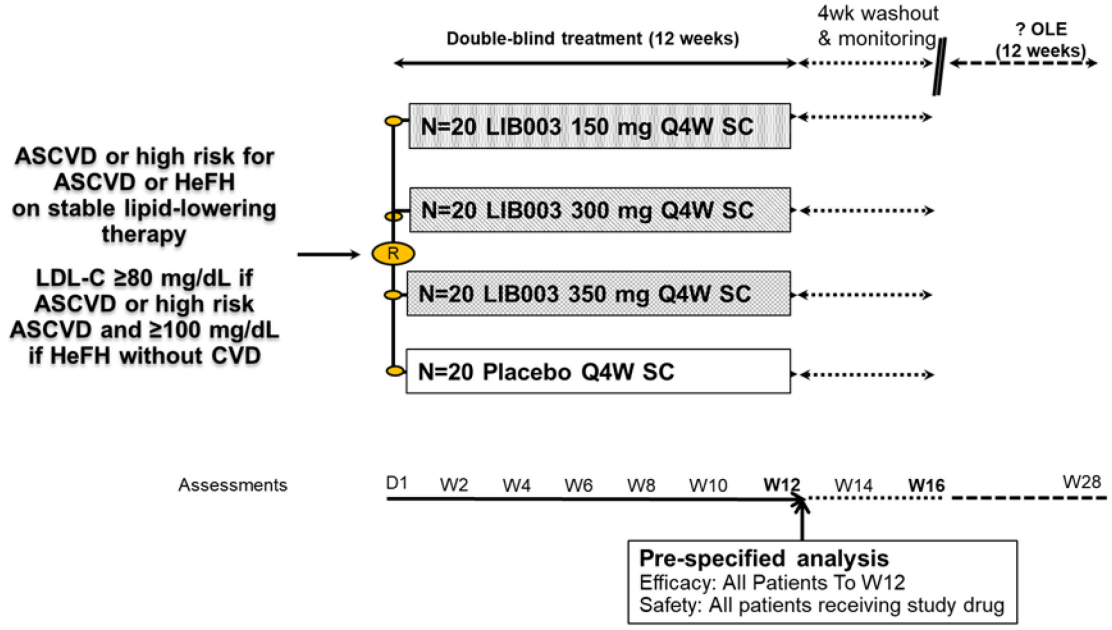
The population for this study includes men and women who are ≥18 years of age with either ASCVD, at high ASCVD risk (≥10% 5-year or ≥7.5% 10-year risk*), and a calculated LDL-C (Friedewald) ≥80 mg/dL (ASCVD or high CVD risk) or ≥100 mg/dL (HeFH and no CVD) and TG ≤400 mg/dL on stable lipid-lowering oral drug therapy (eg, statin with or without ezetimibe). Patients unable to tolerate statins or approved doses of a statin may take lower than approved doses and less frequently than daily as long the dose and dosing frequency is consistent.

** For 10-year risk calculator: https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp. For 5-year risk calculator: https://wa.kaiserpermanente.org/html/public/tools/heart/ (D'Agostino RB Sr, Vasan RS, Pencina MJ,et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-753) OR for 7.5% risk assessment: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/*

STUDY DESIGN AND DURATION:

This is a randomized, double-blind, placebo-controlled, dose-finding, Phase 2 study of 12 weeks duration, followed by a 4-week assessment period. Approximately 80 men and women aged ≥18 years who fulfill the inclusion and exclusion criteria will be enrolled at up to 5 sites in the United States. There will be 3 active and 1 matching placebo treatment groups; In each group there will be 3 LIB003 patients randomized for every 1 placebo patient (ie, 20 LIB003 patients per treatment group and 20 placebo). LIB003 150 mg or placebo will be administered SC Q4W; LIB003 300 mg or placebo will be administered SC Q4W; LIB003 350 mg or placebo will be administered SC Q4W as shown in the figure below.

LIB003-002 Phase 2 Study Design



ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; OLE = optional longer-term extension; Q4W = every 4 weeks; SC = subcutaneous; W = week; wk = week.

Study procedures

Following randomization and dosing on Day 1, patients will be seen in clinic every 2 weeks for 16 weeks; all patients will receive doses of LIB003 or matching placebo on Days 1, 29 (Week 4), and 57 (Week 8). In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified visits during the study. An aliquot of the lipid specimen at randomization will be stored for later analysis of exploratory biomarkers. All lipid, PK, and PCSK9 results from the baseline measurements on Day 1 onward will be blinded to the Investigator and all site and Sponsor personnel involved in the study. Final safety assessments will include adverse events and the results from physical examinations, electrocardiograms (ECGs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. Injection site reactions will be assessed at each visit. An optional longer-term extension study for patients completing the base study is being explored, which would be a separate protocol and require separate informed consent.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

All doses of LIB003 (150 mg, 300 mg, or 350 mg) or matching placebo will be prepared by unblinded pharmacists and administered as a SC injection by unblinded clinic personnel who will not participate further in the evaluation of subjects.

PHARMACOKINETIC VARIABLES:

Pharmacokinetic parameters will include maximum observed concentration (C_{max}), time of maximum observed plasma concentration (T_{max}), serum elimination half-life (T-HALF), area under the serum concentration-time curve (AUC) from time 0 to the time of last quantifiable serum concentration (AUC_{0-t}), AUC across the dosing interval from time of dose to time just prior to the next dose (4 weeks) (AUC_{0-4wks}), AUC from time 0 extrapolated to infinite time (AUC_{inf}), apparent total body clearance (CL/F), and apparent volume of distribution (Vz/F) of total LIB003. Additional PK parameters may be calculated if deemed appropriate.

Total serum PCSK9 concentrations at different time points will also be assessed.

PHARMACODYNAMIC VARIABLES:

The PD parameters include changes in LDL-C (calculated and measured), unbound (free) PCSK9 concentrations, serum lipid parameters [TC, HDL-C, non–HDL-C, VLDL-C, and TG), apo B, apo A1, and Lp(a)].

SAFETY VARIABLES:

Safety assessments will include adverse events and the results of vital sign measurements, ECGs, physical examinations, clinical laboratory tests, and immunogenicity evaluations. Injection site reactions will be monitored by physical examination. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance.

STATISTICAL ANALYSES:

Efficacy Analyses

The co-primary objectives of this study are to assess the percent change from baseline in LDL-C level as the mean of weeks 10 and 12 and at week 12 (both calculated by Friedewald formula) with monthly (Q4W) dosing of various doses of LIB003 administered SC in patients with hypercholesterolemia on stable diet and oral LDL-C-lowering drug therapy. Percent change from baseline in LDL-C will be analyzed with analysis of variance model with treatment as a factor. Other efficacy variables will be analyzed similarly.

Pharmacodynamic Analyses

Pharmacodynamic analysis will be performed based on the PD Population, which is defined as all subjects with any post-baseline PD measurement. Pharmacodynamic and exploratory endpoints will be summarized at each visit, as well as percent change or change from baseline. Inferential analysis may be performed if data grants.

Safety Analyses

The safety endpoint data will be summarized for the Safety Population, which is defined as all subjects who received at least 1 dose of study drug. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the adverse events and serious adverse events (SAEs) will be summarized by overall number of adverse events, severity, and relationship to study drug per treatment group. The number of adverse events leading to withdrawal and SAEs leading to death will also be summarized. The incidence of adverse events will be summarized by system organ class, preferred term, and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged for safety but not efficacy parameters. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest, such as liver function tests, will be summarized.

Vital signs and 12-lead ECGs will also be summarized by visit and by treatment group, along with the changes from baseline. Abnormal physical examination findings will be listed.

Immunogenicity data will be listed. Patients testing positive for LIB003 antibodies will be tested for neutralizing antibodies (NAbs) and titer, and may be further characterized for isotype, binding site, affinity and presence of immune complexes.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered safety related may be asked to return for additional monthly follow-up testing.

In the case of positive NAbs at the final visit (week 16) patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the subject has been followed for a period of at least 12 months. For patients who test positive but have not received active drug follow-up testing will not be required.

SAMPLE SIZE DETERMINATION:

The number of subjects is based on administration of LIB003 in each treatment group achieving a statistically significant ($p<0.01$) 50% reduction in LDL-C at Week 12 compared to the placebo group. In terms of safety, while the number of subjects is not based on statistical consideration there is an 80% probability of observing at least 1 occurrence in a LIB003 treatment group of any adverse event which would occur with a 24% incidence in the population from which the sample is drawn. Approximately 80 patients will participate in this clinical study, including 60 to receive LIB003 and 20 to receive placebo.

SITES: Up to 8 sites in the United States

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
ALT	Alanine transaminase
apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}4wks}$	Area under the serum concentration-time curve across the dosing interval from time of dose to time just prior to the next dose (4 weeks)
$AUC_{0\text{-}t}$	Area under the serum concentration-time curve from time 0 to the time of last quantifiable serum concentration
AUC_{inf}	Area under the serum concentration-time curve from time 0 extrapolated to infinite time
BMI	Body mass index
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CL	Total body clearance
CL/F	Apparent total body clearance
CK	Creatine kinase
C_{max}	Maximum observed plasma concentration
CRA	Clinical Research Associate
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
Enrollment	The day subject signs informed consent and first procedure performed
EPA	Eicosapentaenoic acid
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HSA	Human serum albumin
hs-CRP	High-sensitivity C-reactive protein

Abbreviation	Definition
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
Laboratory manual	Manual provided by the central laboratory containing detailed information on blood volume, sample collection, processing, storage and delivery to the central laboratory
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein (a)
mAb	Monoclonal antibody
NAb	Neutralizing antibody
MABEL	Minimum anticipated biological effect level
NOAEL	No-observed-adverse-effect level
OTC	Over the counter
Pharmacy manual	Manual provided by the Sponsor or CRO containing detailed information on study drug (LIB003 and placebo), receipt and storage, preparation (SC), and drug accountability
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
Q4W	Every 4 weeks
QTcF	Fridericia's Correction Formula
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous(ly)
T-HALF	Terminal elimination half-life
TC	Total cholesterol
TG	Triglycerides
T_{max}	Time of maximum observed plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
Vz/F	Apparent volume of distribution

1 INTRODUCTION AND BACKGROUND INFORMATION

Atherosclerotic cardiovascular disease (ASCVD) is the main cause of morbidity and mortality in industrialized countries and, despite progress in treatment, is projected to cause >22 million deaths over the next 15 years.[1] Low-density lipoprotein cholesterol (LDL-C) has been identified as one of the major, and easily modifiable, risk factors for atherosclerosis.[2] Significant ASCVD benefit has been achieved since the introduction of statin therapy to reduce LDL-C.[2] However, significant unmet medical need remains for additional LDL-C reduction in patients with existing ASCVD and those at increased cardiovascular risk, including patients unable to tolerate statins or effective doses of statins and those with more severe elevations of LDL-C, such as those with familial hypercholesterolemia (FH).[3] Data from the Cholesterol Treatment Trialists' Collaboration has provided evidence that for every 1 mmol/L (~39 mg/dL) reduction in LDL-C, the risk of major cardiovascular events is reduced by 24%, although these data were collected mostly with statins.[2] The recent cardiovascular outcome study with proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAb) and evolocumab (Repatha®) and alirocumab (Praluent®) studies, the FOURIER and ODYSSEY Outcome studies, respectively, have confirmed this relationship for non–statin-lowering of LDL-C.[4,5] Furthermore, recent data from a number of studies, including post hoc analysis of the IMPROVE-IT and Phase 3 alirocumab (Praluent®) studies, plus the FOURIER and SPIRE (Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients) studies, have shown that the relationship between absolute LDL-C reduction and ASCVD event reduction remains linear and extends to very low LDL-C levels of <15 mg/dL without signals of adverse events either from PCSK9 inhibition or very low LDL-C.[6,7,8,9,10,11]

Proprotein convertase subtilisin/kexin type 9 is a circulating protein secreted mainly by the liver that plays a significant role in the recycling of hepatic low-density lipoprotein receptors (LDLRs) and has been identified as a validated drug target for reduction of LDL-C. The LDLR is the primary pathway for LDL-C elimination from circulation; plasma PCSK9 binds to the hepatic LDLR along with LDL-C, targeting the receptor for degradation after endocytosis and thus reducing the expression of LDLRs available to remove LDL-C from circulation. Gain-of-function mutations of PCSK9 are associated with elevated LDL-C and constitute a third cause of FH and accelerated ASCVD, while loss-of-function mutations of PCSK9 are associated with reduced levels of LDL-C and reductions in ASCVD.[4,5,11,12] Adverse effects or other metabolic disturbances have not been observed in subjects carrying loss-of-function PCSK9 mutations, even in a compound heterozygote with no detectable PCSK9 levels and strikingly low LDL-C (14 mg/dL), although recent Mendelian randomization studies have suggested the potential for increased diabetes in patients with impaired glucose tolerance or metabolic syndrome similar to that seen with statins.[5,13,14] Nonclinical studies in PCSK9 knockout or overexpressing mice revealed phenotypes consistent with the human clinical data.[15] Together, the clinical and nonclinical data for the PCSK9 mechanism of action provide a strong genetic proof of concept for targeting PCSK9 to reduce plasma LDL-C levels and lower the risk of coronary heart disease. Based on these observations, PCSK9 inhibition is a promising target for developing new non-mAb therapies for reduction of plasma cholesterol levels.

LIB Therapeutics has developed LIB003, a Chinese hamster ovary-cell line-derived recombinant fusion protein therapeutic agent consisting of a PCSK9-binding domain and human serum albumin (HSA). The HSA contains an alanine substituted for the naturally occurring cysteine at residue 34. The PCSK9-binding domain (Adnectin) in LIB003 is derived from the 10th type III domain of human fibronectin modified by messenger ribonucleic acid display technology to bind selected

targets with high affinity. LIB003 has been designed to target PCSK9 and binds to human PCSK9 with picomolar affinity in a concentration-dependent manner. The binding of LIB003 to PCSK9 blocks the interaction between PCSK9 and LDLR, which thereby prevents LDLR degradation, increases LDLR recycling, enhances LDL-C clearance, and lowers plasma LDL-C levels. Based on this mechanism of action, LIB003 is being developed as an adjunct subcutaneous (SC) therapy for the reduction of LDL-C in patients with homozygous and heterozygous FH (HeFH), ASCVD, or high risk of ASCVD who require additional LDL-C reduction.

Based on in vitro and in vivo data demonstrating that LIB003 was unable to bind rodent PCSK9 with sufficient affinity to modulate pharmacology in wild type rodents, no rodent toxicity studies were performed in accordance with International Council for Harmonisation (ICH) Guideline S6.[16,17,18] To assess the overall toxicity risk of exposing human subjects to LIB003, Good Laboratory Practice (GLP) 4-week repeat-dose and 12-week repeat-dose toxicity studies were conducted in cynomolgus monkeys. These studies demonstrated that LIB003 was clinically well tolerated with no adverse findings at all doses tested (30 mg/kg and 100 mg/kg SC doses; 100 mg/kg intravenous [IV] dose [4-week study only]). The highest dose of 100 mg/kg was considered the no-observed-adverse-effect level (NOAEL) in both studies.

In this current study, as with now numerous studies with mAbs that inhibit PCSK9, inhibition with LIB003 is not expected to adversely impact the cardiovascular system since both PCSK9-null mice and compound heterozygous humans with PCSK9 loss-of-function mutations exhibit no discernable cardiovascular phenotype.[19,20,21] Moreover, extensive clinical studies inhibiting PCSK9 with monoclonal antibodies have shown only cardiovascular benefit.[4,5,7,8,9,10,18,19,20,] Evaluation of the effect of LIB003 on the cardiovascular, central nervous, and respiratory systems were included as part of the 4-week GLP toxicity studies in cynomolgus monkeys in accordance with ICH S6 and S7 Guidances.[16] Results from the study revealed that repeated administration of LIB003 had no effect on cardiovascular, central nervous system, or respiratory function. No genotoxicity studies were conducted with LIB003 as LIB003 is a fusion protein that does not contain an organic linker or any chemical moiety and, therefore, lacks potential for mutagenesis.

LIB003 has been studied in a Phase 1 SAD study of 63 subjects, 45 on LIB003 and 18 placebo, monitored post dose for at least 43 days. Subcutaneous doses of LIB003 25 mg, 75 mg, 150 mg, 300 mg, and 600 mg were administered to healthy subjects on no lipid-lowering therapy who had baseline LDL-C ≥100 and ≤190 mg/dL, and the 150 mg and 300 mg doses were administered to patients on stable statin therapy with baseline LDL-C ≥100 mg/dL. All subjects had TG ≤250 mg/dL. LIB003 was safe and well tolerated following single SC and IV dosing in healthy subjects at all doses both for SC and IV administration as well as in patients with hypercholesterolemia on statin therapy at 150 mg and 300 mg given SC. A summary of adverse events is provided in Table 1 and summarized below.

Table 1. LIB003-001 Summary of Adverse Events

cohort	PBO	25 mg	75 mg	150 mg Diet	300 mg Diet	600 mg SC	300 mg IV	600 mg IV	150 mg Statin	300 mg Statin	ALL LIB
N	18	5	5	5	5	5	5	5	5	5	45
Any TEAE n(%)	6 (33%)	2 (40%)	0 (0%)	1 (20%)	2 (40%)	0 (0%)	2 (40%)	2 (40%)	1 (20%)	2 (40%)	13 (29%)
mild	5	2	0	0	2	0	2	2	1	2	12
moderate	1	0	0	1	0	0	0	0	0	0	1
severe	0	0	0	0	0	0	0	0	0	0	0
Serious AE	0	0	0	0	0	0	0	0	0	0	0
Drug related AE	0	0	0	0	0	0	0	0	0	0	0
ISR	0	0	0	0	0	0	0	0	0	0	0
Common TEAEs											
Cardiac	1	0	0	0	0	0	0	0	0	0	0
Resp Infec	2	2	0	1	0	0	0	0	1	0	4
Gastrointest	1	0	0	0	0	0	1	1	0	0	2
Eye-vision	0	0	0	1	1	0	1	0	0	0	3
MusclSkeletal	2	0	0	0	1	0	0	0	0	0	1
CNS-headache	3	0	0	1	0	0	1	1	0	1	4

There were no deaths or discontinuations due to adverse events.

One placebo treated subject experienced a moderate treatment emergent adverse event (TEAE) that was considered not related to study drug; the subject, a 61-year-old male on statin who received placebo in cohort 9 (LIB003 300 mg SC or placebo group), experienced an episode of syncope with rapid heart rate and was found to be in atrial fibrillation 48 hours following administration of study drug. The patient was transported to the emergency room and admitted to the hospital, but within a few hours spontaneously reverted to sinus rhythm before being seen by a cardiologist and discharged from the hospital. Subsequent follow up with the cardiologist included stress ECHO test and Holter monitoring, which were normal and resulted in no further treatment or intervention.

A total of 6 of 18 (33%) of 18 placebo subjects and 13 of 45 (29%) LIB003 subjects reported at least 1 TEAE; none of the TEAEs were considered serious or drug related (Table 1)

The most common adverse events reported (by more than 1 subject) were respiratory infections, gastrointestinal, eye (blurred vision), CNS (headache) and musculoskeletal; all other adverse events were reported by 1 subject only. None appeared dose related or more frequent in LIB003 treated subjects compared to placebo

One of the adverse events that was considered clinically significant was a 39-year-old male subject who received 300 mg LIB003 IV and experienced swelling of his lips 48 hours after study drug. This was confirmed on examination as mild, not affecting speech, food, or fluid intake. There was no evidence of tongue or soft palate edema and the subject denied any difficulty swallowing or breathing. The subject denied any other symptoms, such as rash or pruritus. There was no evidence of any reaction at the infusion site. He had no history of similar symptoms or known drug or food allergies. His vitals, electrocardiograms (ECGs), and 48-hour safety labs were unremarkable. The subject received oral Benadryl 50 mg and Ranitidine 75 mg (which he continued twice daily [BID]). The Benadryl was replaced with cetirizine 10 mg orally (PO) daily and the subject was monitored as an outpatient after completing Day 4 in the inpatient unit. The swelling subsided after 2 to 3 more days without further intervention.

There were no other clinically remarkable vital sign measurements, physical examination findings, physical measurement findings, or clinically remarkable trends from baseline to discharge.

There were no clinically remarkable trends observed in laboratory findings. A number of subjects in both LIB003 and placebo experienced spikes in CK that were clearly related exercise or excessive or unusual physical activity and CK decreased at subsequent testing.

There were no adverse events based on electrocardiogram (ECG) findings or nor were there any findings that were assessed as clinically significant by the investigator.

Anti-LIB003 antibodies were detected in 2 subjects: One subject treated with 25 mg SC of LIB003 developed low titer ADAs at Day 43; the titers remained low on monthly follow-up, with a stable titer of 160 after 3 months. The second subject was treated with 600 mg IV of LIB003 and developed an ADA response at Day 22, which became progressively more positive, with higher titers by Day 43. The patient was followed at weekly intervals until day 57 when LDL-C returned to within 20% of baseline and will continue to be followed at monthly intervals after day 57 until ADAs become negative or are deemed stable. There were no associated clinical or laboratory adverse effects noted and there did not appear to be any neutralizing impact on efficacy (ie, no neutralizing antibodies [Nabs] although these were not directly tested) as suppression of free PCSK9 and LDL-C reduction, which extended past 43 days, did not appear attenuated compared to other subjects treated with LIB003 in the same cohort.

In summary to date, no specific risks have been identified in the nonclinical or clinical development of LIB003.

1.1 Rationale

This Phase 2 study of LIB003 is designed as a randomized, double-blind, placebo-controlled, dose-finding study of 12 weeks duration, followed by a 4-week assessment period. Approximately 80 men and women aged ≥18 years who fulfill the inclusion and exclusion criteria will be enrolled at up to 5 sites in the United States. There will be 3 active and 1 matching placebo treatment groups; in each group there will be 3 LIB003 patients randomized for every 1 placebo patient (ie, 20 LIB003 patients per treatment group and 20 placebo). LIB003 150 mg or placebo will be administered SC every 4 weeks (Q4W); LIB003 300 mg or placebo will be administered SC Q4W; LIB003 350 mg or placebo will be administered SC Q4W. In a Phase 1 study in both patients on statins and subjects not on statin, all with LDL-C ≥100 mg/dL, single doses of LIB003 150 mg and 300 mg were assessed (Section 4.2 Tables 2, 3 and 4; Figures 2, 3 and 4). The 150 mg dose suppressed free PCSK9 and LDL-C maximally for approximately 4 weeks in subjects not on statins, however the dose did not reduce free PCSK9 or LDL-C sufficiently in all statin treated patients for 4 weeks. The single 300 mg dose, in both non-statin and statin-treated subjects, provided more stable and maximal reductions in free PCSK9, LDL-C, and apo B. In addition, it is anticipated, based on prior data from studies with mAbs, that multiple dosing will result in longer duration of both free PCSK9 suppression and LDL-C reduction. Furthermore, extensive prior data, shows that patients on high intensity statins and those with FH, who have higher baseline PCSK9 levels and likely increased synthesis of PCSK9, will require 300 mg or higher doses in order to suppress both free PCSK9 and LDL C fully for 4 weeks.

Based on these results and an objective of achieving optimal dosing Q4W these 2 doses plus one slightly higher (350 mg) will be explored in a larger group of patients with CVD, high risk for ASCVD or HeFH and treated with a greater range of statins and/or ezetimibe to assess the effect of multiple doses of LIB003 on achieving maximal PCSK9 and LDL-C reduction with Q4W dosing. These doses will be explored in the intended target patient population, patients with

ASCVD, or at high risk for ASCVD who, on stable statin treatment and/or ezetimibe, still have LDL-C levels ≥80 mg/dL or if FH and no CVD, an LDL-C ≥100 mg/dL and triglycerides (TG) ≤400 mg/dL. The enrollment of all of these subjects will support the assessment of the appropriate dose(s) that are effective, safe, and tolerable in a patient population with key characteristics of the target patient population for ultimate use of the medication. Their inclusion in this study will further enable the evaluation of the LDL-C–lowering effects of LIB003 in a statin-treated population in order to select the optimal dose to achieve maximal LDL-C reduction when dosed Q4W. Safety and pharmacodynamic (PD) data derived from the study will support the enrollment of these subjects and dose selection in subsequent Phase 3 studies.

1.2 Risk/Benefit

Subjects will receive no known clinical benefit from participating in the study beyond that of an assessment of their overall health status.

LIB003 at doses up to 600 mg given both SC and IV was shown to reduce LDL-C levels and was safe and well tolerated in a Phase 1 single ascending dose (SAD) clinical study. Two subjects in the phase 1 study developed anti-LIB003 antibodies (ADAs) at doses either below or above the doses to be studied in the phase 2 trial. Neither subject exhibited any adverse clinical or laboratory effects or a reduced LDL-C response. LIB003 has also been well tolerated in nonclinical studies, and the studies conducted to date have demonstrated an acceptable safety profile for LIB003 to support the initiation of this Phase 2 clinical study. Therefore, the risk to subjects in this study is considered low.

2 STUDY OBJECTIVES

2.1 Primary Objective

The co-primary objectives of this study are to assess the percent change from baseline in LDL-C level as the mean of weeks 10 and 12 and at week 12 (both calculated by Friedewald formula) with monthly (Q4W) dosing of various doses of LIB003 administered SC in patients with hypercholesterolemia on stable diet and oral LDL-C-lowering drug therapy.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To re-assess the LDL-C-lowering effects of the primary objectives with LDL-C calculated by Hopkins formula or preparative ultracentrifugation;
- To assess safety and tolerability of various multiple doses of LIB003;
- To assess the PD effects of various multiple doses of LIB003 on plasma unbound (free) PCSK9 concentrations;
- To assess the effects of LIB003 on serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non–HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and TG;
- To assess the effects of LIB003 on apolipoprotein (apo) B, apo A1, and lipoprotein (a) (Lp[a]) serum concentrations;
- To assess the PK of LIB003 and PCSK9 following various multiple doses of LIB003; and
- To assess the frequency of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) following multiple SC doses of LIB003.

2.3 Exploratory Objectives

The exploratory objectives of this study are the following:

- To assess the effect on LDL-C and free PCSK9 6 and 8 weeks after the last dose of LIB003, and
- To assess the effects on other lipid and cardiovascular risk biomarkers as appropriate.

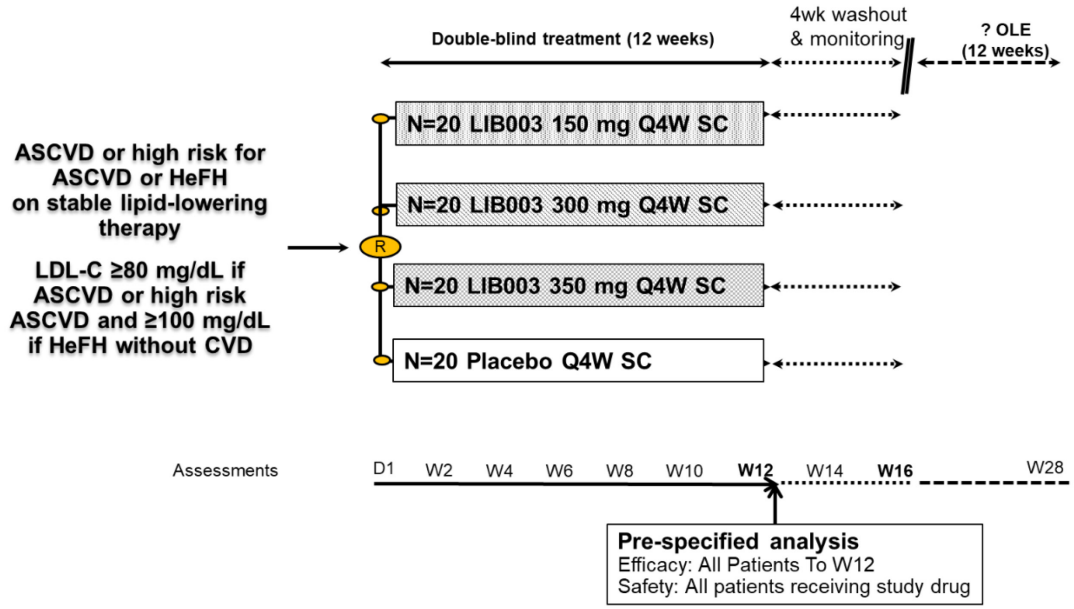
3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled, dose-finding, Phase 2 study of 12 weeks duration, followed by a 4-week follow-up assessment period. Approximately 80 men and women aged ≥18 years who fulfill the inclusion and exclusion criteria will be enrolled at up to 5 sites in the United States. There will be 3 active and 1 matching placebo treatment groups; in each group there will be 3 LIB003 patients randomized for every 1 placebo patient (ie, 20 LIB003 patients per treatment group and 20 placebo). LIB003 150 mg or placebo will be administered SC Q4W; LIB003 300 mg or placebo will be administered SC Q4W; LIB003 350 mg or placebo will be administered SC Q4W as shown in Figure 1 below.

Following randomization and dosing on Day 1, patients will be seen in clinic every 2 weeks for 16 weeks; all patients will receive doses of LIB003 or matching placebo on Days 1, 29 (Week 4), and 57 (Week 8). In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified visits during the study. An aliquot of the lipid specimen at randomization will be stored for later analysis of exploratory biomarkers. All lipid, PK, and PCSK9 results from the baseline measurements on Day 1 onward will be blinded to the Investigator and all site and Sponsor personnel involved in the study. Final safety assessments will include adverse events and the results from physical examinations, ECGs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. Injection site reactions will be monitored by physical examination. Patients testing positive for LIB003 antibodies will be tested for neutralizing antibodies (NAbs) and titers, and may be further characterized for isotype, binding site, affinity and presence of immune complexes. Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered safety related may be asked to return for additional monthly follow-up testing. In the case of positive NAbs at the final visit (week 16) patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the subject has been followed for a period of at least 12 months. For patients who test positive but have not received active drug follow-up testing will not be required. An optional longer-term extension study for patients completing the base study is being explored, which would be a separate protocol and require separate informed consent.

Figure 1. LIB003 Phase 2 Dose ranging Study



ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; OLE = optional longer-term extension; Q4W = every 4 weeks; SC = subcutaneous; W = week; wk = week.

3.2 Stopping Rules

Dose-Limiting Toxicity

Dosing of a subject will be discontinued for any of the following events:

- Alanine transaminase (ALT) and/or aspartate transaminase (AST) >5 × upper limit of normal (ULN) (confirmed by immediate repeat);
- ALT and/or AST >3 × ULN AND total bilirubin >2.0 × ULN for subjects without Gilbert's syndrome and 2 × baseline for those with Gilbert's syndrome (confirmed by immediate repeat);
- ALT or AST >3 × ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic injury, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ≥2 subjects within the same dose group have the same serious adverse event; or
- ≥2 subjects within the same dose group have AST and/or ALT >5 × ULN (confirmed by repeat).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects must meet all the following criteria to be eligible to participate in the study:

1. Provision of written and signed informed consent (by subject) prior to any study-specific procedure;
2. Male or female, ≥18 years of age at screening; women of childbearing potential must be using an effective form of birth control[#] and have a negative pregnancy test at screening.
3. Body mass index (BMI) ≥18 and ≤40 kg/m^2;
4. Prior ASCVD event (ischemic heart disease, stroke, TIA, PVD) or evidence of ASCVD (eg, angiographic, CT calcium [CAC] score >75th percentile[¥] [Appendix C], vascular ultrasound >50% in any arterial bed); OR
5. Patients without ASCVD but considered at high risk for ASCVD (defined as 5-year risk ≥10% based on customized CVD risk calculator[≠], OR 10-year risk ≥7.5% based on ACC/AHA risk calculator[≠], OR aged 40 years and older with diabetes and moderate- to high-intensity statin), OR any patient with a pre-treatment LDL-C ≥190 mg/dL); OR
6. HeFH based on either phenotypic criteria (definite/possible by the Simon Broome Register Group [SBRG] [Appendix A] or definite, probable, or possible by Dutch Lipid Clinic criteria [Table 5]) OR genotyping with DNA-based evidence of mutation in the *LDLR*, *APOB*, or *PCSK9* gene;
7. On appropriate diet and stable dose of statin and/or ezetimibe for at least 4 weeks. Patients documented to be unable to tolerate approved doses of a statin may take lower than approved doses and less frequently than daily as long the dose and dosing frequency is consistent. Patients documented to be unable to tolerate at least 2 statins or ezetimibe may participate. Patients with no ASCVD and aged ≥40 with only DM and no other risk factors who do not meet defined 5- or 10-year CVD risk must be on a moderate- or high-intensity statin;
8. Calculated LDL-C ≥80 mg/dL at screening as determined by the core lab (if ASCVD) or high CVD risk (7.5% 5 year or 10% 10 year) or ≥100 mg/dL if HeFH without CVD. One repeat visit may be performed if LDL-C between 70 and 79 mg/dL for ASCVD/high risk ASCVD or 90 and 99 mg/dL for HeFH without CVD);
9. Fasting TG ≤400 mg/dL as determined by the core lab analysis at screening (one repeat visit may be performed if TG between 401 and 450 mg/dL);
10. Male subjects will either be surgically sterile or agree to use the following forms of contraception: male or female condom with spermicide and a female partner who is sterile or who agrees to use the following contraceptives; diaphragm or cervical cap with spermicide; or intrauterine device, oral, implantable, or injectable contraceptives;

11. Male subjects must refrain from sperm donation until 90 days following the last dose of study drug; and
12. Subject is considered by the Investigator to be otherwise healthy, based on medical and surgical history review, a defined complete physical examination, as well as vital sign measurements, ECGs, and laboratory test results.

[#] *Diaphragm or cervical cap with spermicide or intrauterine device, oral, implantable, or injectable contraceptives*

[≠] *For 10-year risk calculator: https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp. For 5-year risk calculator: https://wa.kaiserpermanente.org/html/public/tools/heart/* (*D'Agostino RB Sr, Vasan RS, Pencina MJ,et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-753) OR for 7.5% risk assessment: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/*

[¥] ***CT coronary calcification score:*** *CAC score ≥75th percentile for age, race and gender: The percentile can be calculated on the MESA website (http://www.mesa-nhlbi.org/Calcium/input.aspx) by inserting the patient CAC score (according to the Agatston method), age, gender, and ethnicity*

References:

National Cholesterol Education Program (NCEP) guidelines recommend intensification of low density lipoprotein cholesterol reduction in patients with multiple risk factors and a CAC score above the 75th percentile. (Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106:3143-421) and Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49-73.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. History of any prior or *concomitant clinical condition* or *acute and/or unstable systemic* disease compromising subject inclusion, *at the discretion of the Investigator*, including but not limited to, the following: a history or presence of clinically significant pulmonary, hepatic, gallbladder or biliary tract, hematologic, gastrointestinal, endocrine (excluding diabetes), immunologic, dermatologic, neurologic, or psychiatric disease, which in the Investigator's opinion would not be suitable for the study from a subject safety consideration or could interfere with the results of the study;
2. Females of childbearing potential not using or willing to use an effective form of contraception[#], or pregnant or breastfeeding, or who have a positive serum pregnancy test at screening;
3. Persistent (confirmed on repeat testing) proteinuria (*greater* than 1+/30 mg/dL on spot testing in a male or non-menstruating female *with greater* than trace hematuria);
4. Homozygous familial hypercholesterolemia;
5. LDL or plasma apheresis within 2 months; lomitapide or mipomersen within 12 months;
6. Uncontrolled cardiac arrhythmia, myocardial infarction, unstable angina, PCI, CABG, or stroke within 3 months prior to enrollment;
7. Planned cardiac surgery or revascularization;

8. NYHA II-IV heart failure;
9. Newly diagnosed (within 3 months of enrollment) or poorly controlled (HbA1c >9%) type 2 diabetes, requiring anti-glycemic or intensification therapy or change in therapy or type 1 diabetes mellitus;
10. Uncontrolled hypertension defined as evidenced by a reproducible (repeated 5 minutes apart) sitting BP ≥160 systolic or ≥100 mmHg diastolic;
11. Subject has taken lipid-regulating drugs other than HMG CoA reductase inhibitors ("statins") or ezetimibe, such as PCSK9 monoclonal antibodies, bile acid sequestering resins, niacin (>500mg/day), or omega-3 fatty acids (>1000 mg/day of EPA/DHA) within 8 weeks of screening visit, or PCSK9- siRNA- or LNA-reducing agents within 12 months of screening, or fibrates or derivatives (within 3 months prior to screening);
12. Subject has taken over-the-counter agents that may alter lipid levels *that are not stable for at least 6 weeks* before screening and are not planned to remain constant through the study. Examples include psyllium preparations including Metamucil® (>2 tbs. per day), niacin (≤500mg/day), plant stanols (such as Benecol®), fish oils (>1000mg/day), and red yeast rice;
13. Subject is taking, or has taken for a *period exceeding 4 weeks*, any of the following drugs in the last 3 months prior to screening: cyclosporine, systemic steroids, Isotretinoin (eg, Accutane®). All other prescription medications will be allowed as long as the dose is stable if for chronic use; HRT use is permitted if initiated at least 2 months prior to the randomization visit and is anticipated to remain stable throughout the study
14. Patients not currently euthyroid as defined by thyroid-stimulating hormone (TSH) below the lower reference range of the central laboratory or >1.5 × the upper reference range for the central laboratory at screening, including patients on stable thyroid replacement therapy;
15. Currently enrolled in another investigational device or drug study, or less than 30 days or 5 half-lives since ending another investigational device or drug study(s), or receiving other investigational agent(s);
16. Subject will not be available for protocol-required study visits or procedures, to the best of the subject's and Investigator's knowledge;
17. Uncontrolled cardiac arrhythmia or prolonged QT at screening (QTcF >450 msec for men and >470 msec for women) or known family history of prolonged QT or unexplained sudden cardiac death;
18. Liver function test at screening (AST or ALT >2 × ULN, total bilirubin >1.5 × ULN [subjects with mild unconjugated hyperbilirubinemia due to Gilbert's syndrome are not excluded], or alkaline phosphatase >2 × ULN based on appropriate age and gender normal values);
19. Unexplained creatine phosphokinase >5 × ULN, unless related to exercise or unusual activity in which case *one repeat test is allowed*;
20. Moderate to severe renal insufficiency defined as serum creatinine > 2.5 mg/dL (221 µmol/L) or an estimated glomerular filtration rate <60 mL/min/1.73 m^2 as determined by the CKD-EPI Equation *on repeat testing*;
21. A history, within 6 months prior to screening, of prescription drug abuse, illicit drug use, or alcohol abuse according to medical history;

22. Has donated or lost a significant volume (>500 mL) of blood or plasma within 30 days prior to randomization;
23. Has had a blood transfusion within 4 weeks of randomization;
24. Was previously treated with LIB003 or any adnectin product;
25. Has a history of *allergy to protein-based biologics* including, but not limited to, mAbs and vaccines;
26. Has a history of any significant drug allergy (such as anaphylaxis or hepatotoxicity or immune-mediated thrombocytopenia or anemia);
27. Has any other finding which, in the opinion of the Investigator, would compromise the subject's safety or participation in the study; or
28. Is an employee or family member of the Investigator or study site personnel.

[#] *Diaphragm or cervical cap with spermicide or intrauterine device, oral, implantable, or injectable contraceptives, male partner with condom or vasectomy.*

4.3 Withdrawal Criteria

Participation of a subject in this clinical study is entirely voluntary and may be discontinued for any of the following reasons:

- The subject withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Requirement of prohibited concomitant medication as outlined above;
- Subject failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

If a subject discontinues prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the study discharge evaluations on Day 113. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

Withdrawn subjects may not be replaced.

4 STUDY TREATMENTS

4.1 Treatment Groups

Following determination of eligibility, approximately 80 subjects will participate in this Phase 2, dose-finding clinical study, including approximately 60 subjects to receive LIB003 and 20 subjects to receive placebo. This study will consist of 3 separate dose groups and 1 placebo group. Patients will be randomized in a 3:1 ratio within each dose group to receive 3 SC doses of LIB003 or placebo for a total of 20 patients on 150 mg, 300 mg or 350 mg of LIB003 or placebo. The study population will include subjects with LDL-C levels ≥80 mg/dL or ≥100 mg/dL based on global CVD risk and TG levels ≤400 mg/dL who are on lipid-lowering therapy consisting of stable tolerated statin therapy and/or ezetimibe.

4.2 Rationale for Dosing

LIB Therapeutics is developing LIB003 with the goal of achieving maximal and stable LDL-C lowering with a 4-week dosing interval. In a Phase 1 SAD study, SC doses of LIB003 25 mg, 75 mg, 150 mg, 300 mg, and 600 mg were administered to healthy subjects not on lipid lowering therapy who had baseline LDL-C ≥100 and ≤190 mg/dL, and the 150 mg and 300 mg doses were administered to patients on stable statin therapy with baseline LDL-C ≥100 mg/dL and triglycerides (TG) ≤250 mg/dL in all subjects. Two additional cohorts of healthy subjects not on lipid lowering therapy with the same lipid entry criteria as their SC cohorts received LIB003 300 mg and 600 mg IV. The study was placebo controlled and double blind. In each cohort there were 5 LIB-003- and 2 placebo-treated patients.

Table 2, Table 3, and Table 4 and Figures 2, 3 and 4 display the results of free PCSK9, LDL-C by preparative ultracentrifugation, and apo B, respectively. Mean reductions in free PCSK9 were rapid with all doses and reached more than 99% within 12 hours and were sustained for at least 3 weeks (Day 22) in the cohorts not on lipid lowering therapy receiving ≥150 mg of LIB003. While the 300 mg dose maintained 99% suppression of free PCSK9 for 29 days, in the 150 mg non-lipid lowering subjects it had decreased to 88% and in those on statins to 46%. The reductions in free PCSK9 were reflected in reductions of LDL-C and apo B where greater reductions were maintained in subjects not on lipid lowering therapy but were not sustained after 3 weeks (Day 22) in patients on statins. The single 300 mg dose, in both non-statin and statin-treated subjects provided stable and maximal reductions in both LDL-C and apo B. It is fully anticipated that patients on statins and also subjects with FH, who have higher baseline PCSK9 levels and increased synthesis of PCSK9, require 300 mg or higher doses in order to suppress both free PCSK9 and LDL-C fully for 4 weeks. It is also anticipated that multiple doses of LIB003 will provide longer duration of efficacy.

Table 2. LIB003-001 Baseline and Percent Change in Free PCSK9 Concentrations by Treatment

cohort	PBO	25 mg	75 mg	150 mg Diet	300 mg Diet	600 mg SC	300 mg IV	600 mg IV	150 mg Statin	300 mg Statin
N	18	5	5	5	5	5	5	5	5	5
baseline ng/mL										
mean (SD)	219 (107)	200 (48)	170 (23)	211 (56)	206 (36)	178 (41)	195 (54)	173 (35)	230 (41)	240 (36)
% ↓ mean (min:max)										
day 2	-9 (-44:36)	-88 (-99:-49)	-91 (-99:-56)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-98)	-99 (-99:-99)
day 8	-6 (-46:102)	-79 (-97:-28)	-88 (-99:-46)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)
day 15	15 (-57:76)	-45 (-65:-23)	-85 (-99:-28)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)
day 22	-6 (-54:33)	-21 (-53:11)	-79 (-96:-49)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-91 (-99:-63)	-95 (-99:-81)
day 29	-6 (-58:68)	-11 (-53:69)	-54 (-82:-39)	-88 (-99:-63)	-99 (-99:-97)	-99 (-99:-99)	-99 (-99:-99)	-99 (-99:-99)	-46 (-78:-26)	-70 (-99:-23)
day 36	-3 (-55:56)	-20 (-44:20)	-28 (-59:-15)	-59 (-98:-16)	-88 (-99:-47)	-99 (-99:-99)	-92 (-99:-83)	-98 (-99:-98)	-26 (-59:0)	-46 (-99:-18)
day 43	0 (-48:65)	-18 (-50:18)	-17 (-34:-3)	-49 (-87:-20)	-88 (-99:-50)	-97 (-99:-89)	-58 (-98:-34)	-95 (-97:-90)	-9 (-48:20)	-29 (-94:4)

Figure 2. LIB003-001 SAD: Changes in free PCSK9 with LIB003 by treatment

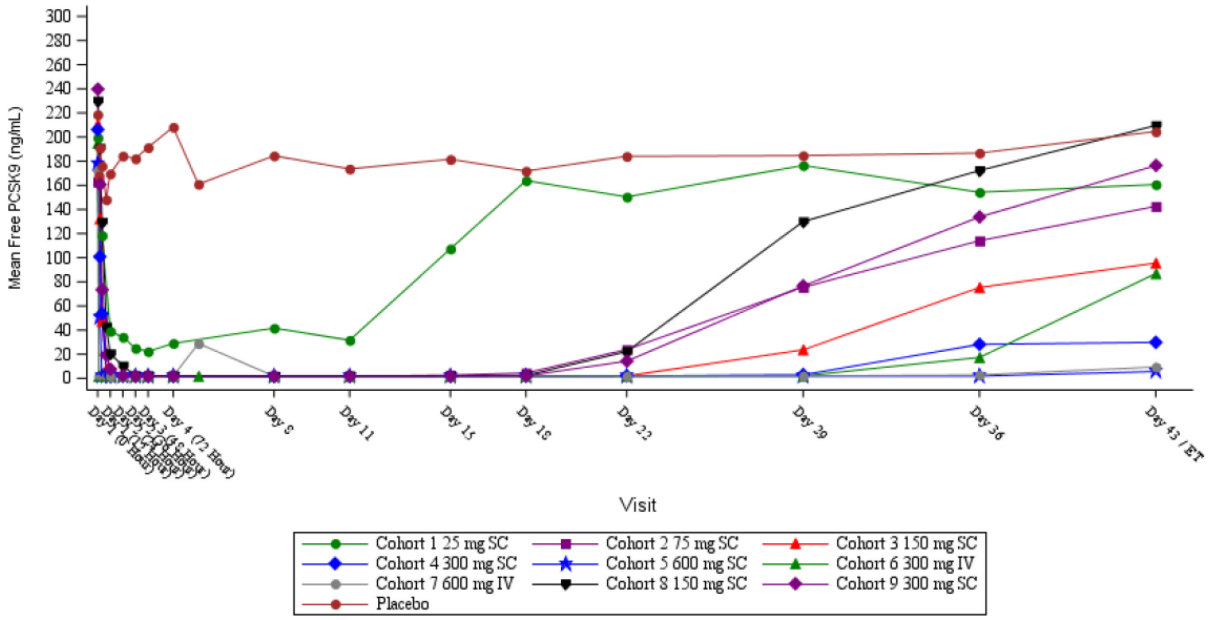


Table 3. LIB003-001 Baseline and Percent Change in PUC LDL-C Concentrations by Treatment

cohort	PBO	25 mg	75 mg	150 mg Diet	300 mg Diet	600 mg SC	300 mg IV	600 mg IV	150 mg Statin	300 mg Statin
N	18	5	5	5	5	5	5	5	5	5
baseline mg/dL										
mean (SD)	134 (27)	127 (23)	129 (32)	133 (21)	127 (18)	128 (14)	114 (21)	128 (14)	126 (19)	117 (15)
% ↓ mean (min:max)										
day 8	-2 (-32:38)	-28 (-40:-2)	-32 (-47:-2)	-43 (-66:-28)	-30 (-46:-13)	-38 (-51:-25)	-47 (-61:-29)	-51 (-62:-41)	-54 (-79:-44)	-53 (-72:-26)
day 15	-4 (-24:22)	-20 (-30:-11)	-37 (-59:10)	-52 (-69:-40)	-43 (-65:-20)	-55 (-71:-41)	-59 (-67:-48)	-64 (-76:-48)	-66 (-82:-49)	-68 (-78:-56)
day 29	-3 (-31:39)	-14 (-59:11)	-17 (-30:20)	-43 (-58:-30)	-50 (-72:-39)	-58 (-67:-49)	-62 (-72:-51)	-65 (-76:-50)	-36 (-48:-20)	-47 (-77:-15)
day 43	-3 (-29:39)	-12 (-18:-6)	-10 (-25:20)	-18 (-31:-6)	-37 (-68:-12)	-50 (-63:-39)	-17 (-40:-30)	-60 (-70:-44)	-11 (-35:8)	-3 (-77:34)

Figure 3. LIB003-001 SAD: Changes in ultracentrifugation LDL-C by treatment

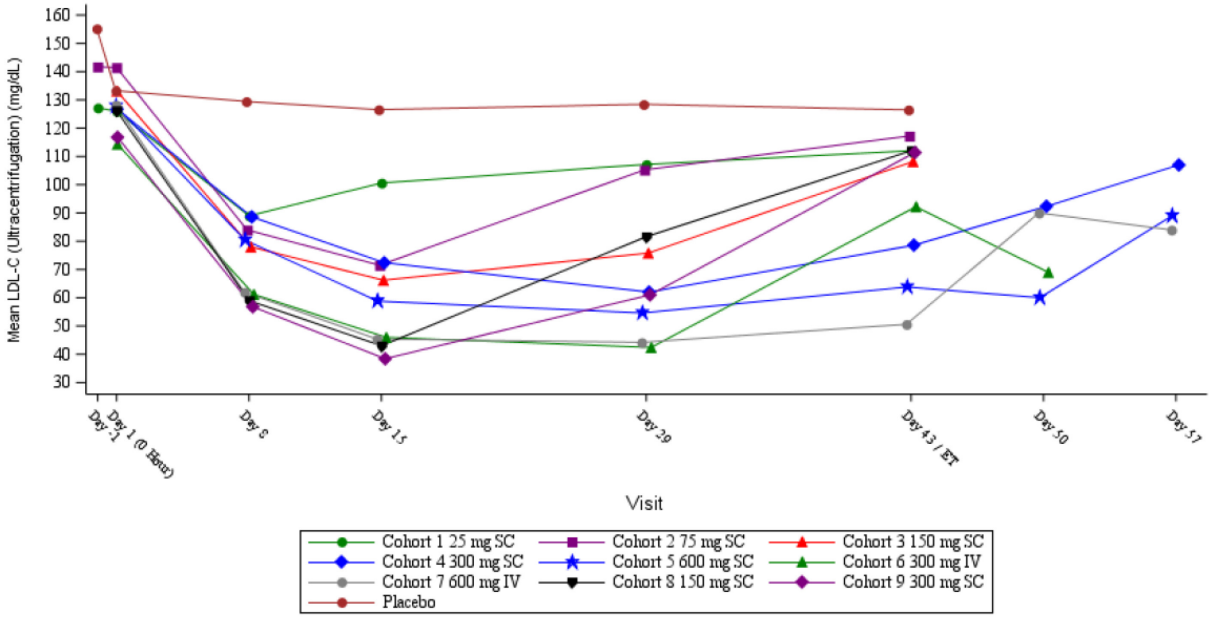
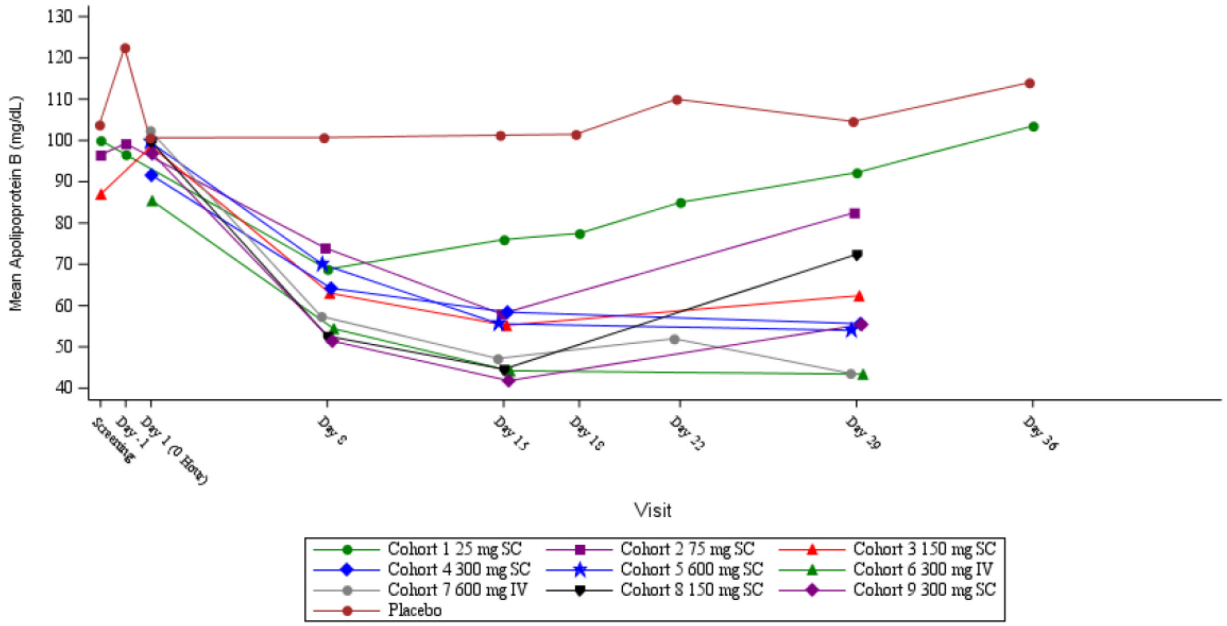


Table 4. LIB003-001 Baseline and Percent Change in Apo B Concentrations by Treatment

cohort	PBO	25 mg	75 mg	150 mg Diet	300 mg Diet	600 mg SC	300 mg IV	600 mg IV	150 mg Statin	300 mg Statin
N	18	5	5	5	5	5	5	5	5	5
baseline mg/dL										
mean (SD)	106 (16)	97 (8)	92 (22)	99 (6)	92 (13)	100 (8)	85 (12)	102 (14)	100 (10)	97 (9)
% ↓ mean (min:max)										
day 8	-4 (-29:31)	-29 (-33:-26)	-18 (-23:11)	-37 (-56:-20)	-29 (-43:-12)	-30 (-42:-19)	-30 (-42:-19)	-35 (-48:-17)	-47 (-67:-40)	-48 (-59:-23)
day 15	-3 (-19:28)	-22 (-27:-18)	-31 (-51:7)	-44 (-56:-33)	-35 (-58:-11)	-45 (-57:-36)	-47 (-57:-36)	-53 (-67:-35)	-55 (-66:-42)	-57 (-64:-49)
day 29	0 (-30:20)	-5 (-16:6)	-11 (-23:6)	-37 (-52:-24)	-38 (-59:-23)	-46 (-54:-41)	-48 (-56:-37)	-56 (-66:-37)	-28 (-38:-13)	-43 (-67:-21)

Figure 4. LIB003-001 SAD: Changes in Apo B by treatment



Based on these data, the doses selected for Q4W dosing in this Phase 2, dose-finding study include 150 mg, 300 mg, and 350 mg. All 3 doses are anticipated to be safe based on the lack of adverse event findings at both human LIB003 exposure in Phase 1 up to 600 mg both SC and IV and levels achieved in the 12-week non-human primate GLP toxicology study. Two subjects in the phase 1 study developed anti-LIB003 antibodies (ADAs) at doses either below or above the doses to be studied in the phase 2 trial. Neither subject exhibited any adverse clinical or laboratory effect or a reduced LDL-C response.

4.3 Randomization and Blinding

This study follows a randomized, double-blind, placebo-controlled design. Within each dosing group subjects will be randomized in a 3:1 ratio within each dose group to receive 1 of 3 doses of LIB003, 150 mg, 300 mg, or 350 mg dose or placebo on Days 1, 29, and 57 according to a computer-generated randomization scheme. Because the color of the study drug product and placebo will not be identical, all therapy will be prepared by an unblinded pharmacist and administered by unblinded nurses who will be instructed not to discuss randomized treatment assignments. Neither the pharmacist nor nurse(s) administering the study drug will be involved in any other aspects of the study or subject contact.

In addition to the treatment blind, all lipid, ADA, PK, and PCSK9 results from the baseline measurements on Day 1 onward will be blinded to the Investigator and study personnel involved in the study at both the clinical site and LIB Therapeutics.

4.4 Breaking the Blind

At the initiation of the study, the Investigator will be instructed on the method for breaking the blind. Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety. Unblinding at the clinical site for any other reason will be considered a protocol deviation. The Investigator should contact the Medical Monitor before breaking the blind, if time permits. When the blind is broken, the reason must be fully documented.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt to preserve the blind is made.

4.5 Drug Supplies

4.5.1 Formulation and Packaging

The drug product is a 250 mg/mL solution packaged in 0.85 mL volumes in 2 mL clear glass vials with stoppers and aluminum crimp seals.

The LIB003 formulation contains 20 mM histidine, 150 mM sodium chloride, 0.02% Polysorbate 80 at pH 6.8, which are common excipients at concentrations used in approved protein therapeutics administered as SC doses.

4.5.2 Study Drug Preparation and Dispensing

Trained medical personnel will administer LIB003 or placebo to subjects within the clinical facility. Site personnel should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by LIB Therapeutics

as outlined in the pharmacy manual. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact LIB Therapeutics immediately.

Instructions for LIB003 preparation are documented in a separate pharmacy manual.

4.5.3 Study Drug Administration

Study drug (LIB003 or matching placebo) will be administered by SC injection on Days 1, 29, and 57. Study drug will be administered under the supervision of the unblinded site personnel who will not be involved in further subject assessments.

Dosing instructions as well as materials required for storage, preparation, and administration are documented in the separate pharmacy manual.

4.5.4 Treatment Compliance

Treatment compliance will be dependent on the preparation and administration of study drug by the unblinded site personnel.

4.5.5 Storage and Accountability

Study Drug will be stored in a secure, temperature-controlled location. Study drug will only be prepared and dispensed by an authorized unblinded pharmacist at the clinical site. Any deviation from storage conditions must be reported immediately to the Investigator and LIB Therapeutics Medical Monitor.

Site personnel will maintain accurate records of receipt and condition of study drug upon receipt. In addition, accurate records of each dose dispensed to each subject will be kept on a study drug accountability log.

Study drug accountability records will be maintained by the unblinded pharmacist in a secure location. Drug accountability records will be available for verification by unblinded LIB personnel.

Storage and accountability information will be outlined in the separate pharmacy manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Concomitant therapy includes all medications and non-medication interventions used by a subject during the study.

Medications include prescription drugs, over-the-counter (OTC) drugs, approved dietary and herbal supplements, and nutritional supplements. Examples of non-medication interventions include individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy. All concomitant medications and non-medication interventions should be reported to the Investigator and recorded in the concomitant medications eCRF.

As a general rule, concomitant medications will be permitted unless specifically excluded and provided they are anticipated to remain stable throughout the study or do not impact LDL-C. The

rationale for use of any exceptions is to be discussed between the Investigator and the Sponsor and clearly documented. The following medications are exceptions:

- Medications used to treat adverse events may be prescribed preferably after consultation with the Medical Monitor, unless there is an immediate medical need to ensure the well-being of the subject that should not be delayed. All therapy and/or medication administered to manage adverse events should be recorded in the appropriate eCRF;
- Hormone replacement therapy use is only permitted if initiated at least 2 months prior to the randomization visit and is anticipated to remain stable throughout the study.

Any other investigational drug taken within 30 days or 5 half-lives (whichever is longer) prior to screening is excluded.

5.6.2 Restricted Medications and/or Procedures

Restricted medications include, but are not limited to, the following:

- Use of, or treatment with, any prescription lipid-altering drugs (other than statins and ezetimibe as specified above).

5.6.3 Restrictions and Dietary Guidelines

Subjects should be encouraged to continue on appropriate and same diet and not participate in strenuous physical activity or exercise from 48 hours prior to all study visits to prevent concomitant increases in creatine kinase and throughout the duration of the study.

Subjects are requested to refrain from using alcohol for the 24-hour period prior to clinic visits due to potential impact on serum lipids.

Fasting is defined as no food or caloric beverages for at least 10 hours. Subjects will be permitted and encouraged to drink water ad libitum.

5.6.4 Documentation of Prior and Concomitant Medication Use

The Investigator should record the use of all concomitant medications taken during the study, including statin, statin dose and/or ezetimibe plus adherence, both prescribed and OTC, in the eCRF and the source document. This includes drugs used on a chronic and as-needed basis. Subjects should be discouraged from starting any new medication, both prescribed and OTC, without consulting the Investigator, unless the new medication is required for an emergency or common ailments such as headache, upper respiratory infection and constipation.

6 STUDY PROCEDURES

6.1 Informed Consent

Written informed consent for the study will be obtained from all subjects before any protocol specific procedures are performed. The Investigator must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding the clinical study in which they volunteer to participate.

6.2 Study Schedule

A ±3-day window is allowed for all clinic visits; unanticipated or unavoidable cancellations due to weather or public holidays occur visits may be scheduled within a 5-day window and will not be considered protocol deviations if appropriately documented. The screening visit should be performed between 7 and 28 days prior to the randomization visit.

All blood samples should be collected while the subject is in a fasted state (≥10 hours) and prior to administration of study drug (LIB003 or placebo).

6.2.1 Screening Period (Day-7 to -28)

Screening procedures must be performed no earlier than 7 days and no later than 28 days prior to dosing and include the following:

- Obtain informed consent;
- Evaluate inclusion/exclusion criteria;
- Obtain demographics and medical history;
- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Perform physical examination;
- Measure height and weight and calculate BMI;
- Perform 12-lead ECG;
- Record vital signs;
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
    - Full safety chemistry, hematology, and TSH,
    - Brief lipid panel, and
    - Serum pregnancy test (only women of childbearing potential); serum follicle-stimulating hormone (FSH) will be measured for women uncertain of post-menopausal status (<1 year since last menses).

6.2.2 Study Day 1

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Obtain body weight;
- Perform physical examination (if the screening physical examination is performed within 14 days of the randomization visit, it does not need to be repeated);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
  - Full safety chemistry and hematology;
  - Expanded lipid panel;
  - PK;
  - PCSK9 (total and free) (pre-dose);
  - Immunogenicity (pre-dose); and
  - Exploratory biomarkers (pre-dose);
- Randomize eligible subjects;
- Administer SC dose of study drug;
- Assess injection site (pre-dose and 15 mins post-dose); and
- Assess adverse events.

6.2.3 Study Day 15

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect fasting blood samples for the following:
  - Brief safety chemistry,
  - Brief lipid panel,
  - PK,
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

6.2.4 Study Day 29

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis,
- Collect fasting blood samples for the following:
  - Full safety chemistry and hematology,
  - Expanded lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity, and
- Administer SC dose of study drug;
- Assess injection site; and (pre-dose and 15 mins post-dose);
- Assess adverse events.

6.2.5 Study Day 43

The following procedures will be performed:

- Record prior and concomitant medications; including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect fasting blood samples for the following:
  - Brief safety chemistry,
  - Brief lipid panel,
  - PK,
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

6.2.6 Study Day 57

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
- Collect fasting blood samples for the following:
  - Full Safety chemistry and hematology,
  - Expanded Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Exploratory biomarkers,
  - Immunogenicity,
- Administer SC study drug;
- Assess injection site (pre-dose and 15 mins post-dose); and
- Assess adverse events.

6.2.7 Study Day 71

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect fasting blood samples for the following:
  - Brief safety chemistry,
  - Brief lipid panel,
  - PK,
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

6.2.8 Study Day 85

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Perform physical examination;
- Obtain body weight
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
  - Full safety chemistry and hematology;
  - Expanded lipid panel;
  - PK;
  - PCSK9 (total and free);
  - Immunogenicity; and
  - Exploratory biomarkers (pre-dose);
- Assess injection site; and
- Assess adverse events.

6.2.9 Study Day 99

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect fasting blood samples for the following:
  - Brief safety chemistry,
  - Brief lipid panel,
  - PK,
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

6.2.10 Study Day 113/Early Termination Visit

The end of study for subjects completing is Day 113. For subjects who are withdrawn from the study prior to completion, all Day 113 procedures will be performed at an early termination visit. The procedures performed include the following:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month;
- Perform physical examination (ONLY if Early Termination) and obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- 12-lead ECG (ONLY if Early Termination);
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
  - Full safety chemistry and hematology,
  - Serum pregnancy test (women of childbearing potential only); serum FSH will be measured for women uncertain of post-menopausal status (<1 year since last menses),
  - Expanded lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity, and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

6.2.11 Follow-up Visit for positive ADAs/NaBs

Subjects positive for binding, non-neutralizing antibodies with clinical sequelae that are considered safety related at final visit (week 16) may be asked to return for additional monthly follow-up testing.

Patients with positive NAbs at the final visit (week 16) patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the subject has been followed for a period of at least 12 months. For patients who test positive but have not received active drug follow-up testing will not be required.

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose and/or ezetimibe plus adherence for prior month; Assess adverse events since last visit
- Obtain body weight
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;

- Collect fasting blood samples for the following:
  - Full safety chemistry and hematology;
  - Brief lipid panel;
  - PCSK9 (total and free);
  - Immunogenicity; and
- Assess injection site; and

7 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

All blood samples should be collected while the subject is in a fasted state (≥10 hours ad lib water is allowed and encouraged) and prior to administration of LIB003 or placebo. After the scheduled analyses are completed, residual samples may be utilized for further exploratory analyses. Instructions for specimen collection and storage are detailed in the laboratory manual.

Detailed instructions for collection, processing, packaging, and shipping of all blood samples will be provided to the site in the laboratory manual.

7.1 Pharmacokinetic Parameters

Pharmacokinetics of LIB003 and PCSK9 will be derived from serum concentration-versus time data. The actual PK sampling times will be captured in the eCRF.

Pharmacokinetic parameters will include the following:

- C_{max} – maximum observed plasma concentration,
- T_{max} – time of maximum observed plasma concentration,
- AUC_{0-t} – area under the serum concentration-time curve from time 0 to the time of last quantifiable serum concentration,
- AUC_{0-4wks} – area under the serum concentration-time curve across the dosing interval from time of dose to time just prior to the next dose (4 weeks),
- AUC_{inf} – area under the serum concentration-time curve from time 0 extrapolated to infinite time,
- T-HALF – serum elimination half-life,
- CL/F – apparent total body clearance, and
- Vz/F – apparent volume of distribution.

Pharmacokinetic parameters for the 150 mg, 225 mg, and 300 mg doses will be measured at the time points specified in Table 6. Additional PK parameters may be calculated if deemed appropriate.

Total serum PCSK9 concentrations at different time points will also be assessed.

7.2 Pharmacodynamic Endpoints

The co-primary endpoints are the percent change from baseline in LDL-C level as the mean of weeks 10 and 12 and at week 12 (both by Friedewald formula) for each LIB003 dose compared to the placebo.[22-24] Percent change from baseline in LDL-C will be analyzed with analysis of variance model with treatment as a factor. The co-primary endpoints will be repeated on LDL-C calculated by Hopkins formula or preparative ultracentrifugation.

The secondary objectives to assess the PD effects of differing multiple doses of LIB003 will be measured by the following secondary endpoints:

- Serum unbound (free) PCSK9 concentrations and serum LDL-C by both preparative ultracentrifugation and d Hopkins formula[25];

- Serum lipids, including TC, HDL-C, non–HDL-C, VLDL-C, and TG; and
- Apo B, apo A1, and Lp(a) serum concentrations.

7.2.1 Immunogenicity Endpoints

Another secondary objective is to assess the occurrence and frequency of ADAs following multiple doses of LIB003. Anti-LIB003 antibodies will be measured at the time points specified in section 8.8 and Table 6.

7.2.2 Exploratory Endpoints

Exploratory objectives include:

- The effects of different doses of LIB003 on other lipid and cardiovascular risk biomarkers as appropriate may be assessed from saved, stored, frozen serum aliquots obtained at the time points specified in Table 6 (Appendix C).
- An assessment of the cumulative effect of 3 different doses on free PCSK9, LDL-C, and apo B for 6 and 8 weeks after the final dose.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of randomization until study participation is complete. Subjects should be instructed to report any adverse event that they experience to the Investigator. From the time of randomization, the Investigator should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at randomization should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at randomization and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

8.2.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (ie, the relationship cannot be ruled out).

8.2.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.2.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity:

- Mild – An event that is easily tolerated and generally not interfering with normal daily activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.
- Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration – The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases – Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant drug – The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug – Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses – The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug – The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.3 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
    - NOTE: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
    - NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.4 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report a SAE, fax the completed SAE form to Medpace (fax number listed below) within 24 hours of awareness.

Safety Contact Information: Medpace Clinical Safety
Medpace SAE reporting line – USA:
Telephone: +1-800-730-5779, dial 3 or 513-579-9911, dial 3
Fax: +1-866-336-5320 or 513-579-0444
e-mail: medpace-safetynotification@medpace.com

Follow-Up Reports

The Investigator must continue to follow subject(s) until a SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (eg, subject discharge summary or autopsy reports), should be faxed to Medpace Clinical Safety.

8.5 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and Early Termination study procedures will be performed.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the FDA and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor will also inform all Investigators as required.

8.7 Clinical Laboratory Evaluations

Clinical laboratory profiles for lipids, hematology, serum chemistry, and urinalysis will be evaluated from samples collected after ≥10 hours of fasting (ad lib water is allowed and encouraged) at the time points specified in Table 6 (Appendix C).

For all women of childbearing potential, a serum pregnancy test will be performed at screening and the end of study visit (Day 113/Early Termination). Serum FSH will be measured for women uncertain of post-menopausal status (<1 year since last menses).

A complete list of laboratory analyses to be performed is presented in Appendix D.

8.7.1 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs that meet the following criteria, must be reported as SAEs:

1. ALT or AST levels >3 × ULN; and
2. Total bilirubin levels >2 × ULN, without initial findings of Gilbert's syndrome or cholestasis (elevated serum alkaline phosphatase); and
3. No other immediately apparent possible causes of ALT or AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.8 Immunogenicity

Subjects will be assessed for ADAs at designated study visits specified as follows and also in Table 6 (Appendix C). Patients testing positive for LIB003 antibodies will be tested for neutralizing antibodies (NAbs) and titer, and may be further characterized for isotype, binding site, affinity and presence of immune complexes.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered safety related may be asked to return for additional monthly follow-up testing.

In the case of positive NAbs at the final visit (week 16) patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the subject has been followed for a period of at least 12 months. For patients who test positive but have not received active drug follow-up testing will not be required.

8.9 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at designated study visits specified in Table 6 (Appendix C). Blood pressure and heart rate will be measured after the subject has been seated or supine for ≥5 minutes.

8.10 Electrocardiograms

Twelve-lead (single) ECGs will be assessed at designated study visits specified in Table 6 (Appendix C). Subjects should be resting in the supine position for ≥10 minutes prior to each 12-lead ECG.

8.11 Physical Examinations

Physical examinations will be performed throughout the study at the time points specified in Table 6 (Appendix C). Injection site reactions will be monitored by examination of injection site.

9 STATISTICS

9.1 Statistical Methods

9.1.1 Analysis Populations

The PK Evaluable Population is defined as all subjects with valid PK parameters (C_{max} and AUC).

The PD Population is defined as all subjects who received at least 1 dose of study drug and with any post-baseline PD measurement.

The Safety Population is defined as all subjects who received at least 1 dose of study drug.

9.1.2 Analysis of Efficacy

The co-primary endpoints are the percent change from baseline in LDL-C level at the mean of weeks 10 and 12 and at week 12 (both by Friedewald formula) for each LIB003 dose compared to the placebo.[22-24] Percent change from baseline in LDL-C will be analyzed with analysis of variance model with treatment as a factor. Other efficacy variables will be analyzed similarly.

9.1.3 Pharmacodynamic Analysis

Pharmacodynamic analysis will be performed based on the PD Population. Pharmacodynamic endpoints will be summarized at each visit, as well as percent change or change from baseline.

Exploratory endpoints will be summarized at each visit, as well as percent change or change from baseline. Inferential analysis may be performed if data grants.

9.1.5 Immunogenicity analyses

Immunogenicity data will be listed.

9.1.6 Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed based on the PK Evaluable Population. Power Law model will be used to assess the dose proportionality for the LIB003 treatment groups. All PK parameters and PK concentrations will be summarized descriptively.

9.1.7 Analysis of Safety

The safety endpoint data will be summarized for the Safety Population. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the adverse events and SAEs will be summarized by overall number of adverse events, severity, and relationship to study drug per treatment group. The number of adverse events leading to withdrawal and SAEs leading to death will also be summarized. The incidence of adverse events will be summarized by system organ class, preferred term, and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from baseline. The values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values that are identified as being clinically significant will be flagged. Laboratory abnormalities of special interest, such as liver function tests and antidrug antibodies, will be summarized.

Vital signs and 12-lead ECGs will also be summarized by visit and by treatment group, along with the changes from baseline. Abnormal physical examination findings will be listed.

9.1.8 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

9.1.9 Interim Analysis

No interim analysis is planned for this study.

9.2 Sample Size Determination

The number of subjects is based on administration of LIB003 in each treatment group achieving a statistically significant ($p<0.01$) 50% reduction in LDL-C at Week 12 compared to the placebo group. In terms of safety while the number of subjects is not based on statistical consideration there is an 80% probability of observing at least 1 occurrence in a LIB003 treatment group of any adverse event which would occur with a 24% incidence in the population from which the sample is drawn. Approximately 80 patients will participate in this clinical study, including 60 to receive LIB003 and 20 to receive placebo.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (CFR) (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

The latest version of the Medical Dictionary for Regulatory Activities for medical history and adverse events. The latest versions of the World Health Organization Drug Dictionary will be used for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The Institutional Review Board (IRB) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and ICH require that approval be obtained from an IRB prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB.

No drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs

and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

The Investigator is required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, the Investigator must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigator by Medpace or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

12.2 Address List

12.2.1 Sponsor

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13 REFERENCES

1. Mathers C, Loncar Dejan. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3:e442.
2. Cholesterol Treatment Trialists' Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-1681.
3. Turner T, Raal F, Stein E. Evolving targets of therapy: proprotein convertase subtilisin/kexin 9 inhibition. In: Ballantyne C, eds. Clinical lipidology: a companion to Braunwald's heart disease. 2nd ed. 2014;346-357. Elsevier.
4. Sabatine M, Guigliano R, Keech A, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017:1-10.
5. Steg PG, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab - ODYSSEY OUTCOMES. Presented at American College of Cardiology Annual Scientific Session, Orlando, FL, March 10, 2018. http://www.acc.org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes
6 Giugliano RP, Wiviott SD, Blazing MA, et al. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT Trial. JAMA Cardiol. 2017. [Epub ahead of print].
7. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in atherogenic lipids and major cardiovascular events: a pooled analysis of 10 ODYSSEY trials comparing alirocumab to control. Circulation. 2016;134:1931-1943.
8 Ridker P, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med. 2017:1-13.
9. Cannon CP, Blazing MA, Giugliano, RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387-2397.
10. The Lipid Research Clinics Coronary Primary Prevention Trial Results I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351-364.
11. Giugliano RP, Pedersen TR, Park JG et al Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. Lancet 2018;390:1962–1971
12 Seidah N, Prat A. The biology and therapeutic targeting of the proprotein convertases. Nat Rev Drug Discov. 2012;11:367-383.
13. Abifadel M, Varret M, Rabes J, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154-156.
14. Cohen J, Boerwinkle E, Mosley T Jr., et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354:1264-1272.
15. Ference B, Robinson J, Brook R, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. N Engl J Med. 2016;375:2144-2153.
16. Schmidt A, Swerdlow D, Holmes M, et al. PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study. Lancet Diabetes Endocrinol. 2017;5:97 105.
17. Rashid S, Curtis D, Garuti R, et al. Decreased plasma cholesterol and hypersensitivity to statins in mice lacking PCSK9. Proc Natl Acad Sci USA. 2005;102:5374-5379.
18. Pharmacodynamics of PCSK9 adnectins BMT-260570 and BMT-260571. Bristol-Myers

Squibb Company; 2016. Document Control No. 930103488.
19. Pharmacokinetics of a test article following administration to CD1 male mice with pharmacokinetic time points through 72 hours. LIB Therapeutics; 2017. Testing Facility Study Number: 20104650.
20. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline S7A: Safety pharmacology studies for human pharmaceuticals. 2000.
21. Scamuffa N, Calvo F, Chrétien M, Seidah NG, Khatib AM. Proprotein convertases: lessons from knockouts. Faseb J. 2006;1954-1963.
22. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 Monotherapy for Hypercholesterolemia: The MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63(23):2531-2540.
23. Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014;311(18):1870-1882.
24. Raal FJ, Stein EA, DuFour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:331-340
25. Martin SS, Giugliano RP, Murphy SA, et al. Comparison of low-density lipoprotein cholesterol assessment by Martin/Hopkins Estimation, Friedewald Estimation, and Preparative Ultracentrifugation: Insights from the FOURIER Trial. JAMA Cardiol. 2018.1533 [Epub ahead of print].

APPENDIX A: SIMON BROOME CRITERIA

Definite Familial Hypercholesterolemia:

Required laboratory = high cholesterol levels:

- Adult = Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)
- Child less than 16 years of age = Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)

Plus at least one of the two:

1. Plus physical finding = tendon xanthomas, or tendon xanthomas in first or second degree relative

OR

2. DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Possible Familial Hypercholesterolemia

Laboratory = high cholesterol levels:

- Adult = Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L)
- Child less than 16 years of age = Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L)

Plus at least one of the two:

1. Family history of at least one of the following.
    - Family history of myocardial infarction at:
        - Age 60 years or younger in first degree relative
        - Age 50 years or younger in second-degree relative

OR

2. Family history of elevated total cholesterol
    - Greater than 290 mg/dL (7.5 mmol/L) in adult first- or second-degree relative
    - Greater than 260 mg/dL (6.7 mmol/L) in child, brother or sister aged younger than 16 years.

1. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *American journal of epidemiology.* 2004;160:407-420.

APPENDIX B: DUTCH LIPID CLINIC CRITERIA

Table 5. Dutch Lipid Clinic Criteria

	Points
Criteria **Family history**	
First-degree relative with known premature* coronary and vascular disease, OR First-degree relative with known LDL-C level above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR Children aged less than 18 years with LDL-C level above the 95th percentile	2
Clinical history	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels mg/dl (mmol/liter)	
LDL-C >= 330 mg/dL (≥8.5)	8
LDL-C 250 – 329 mg/dL (6.5–8.4)	5
LDL-C 190 – 249 mg/dL (5.0–6.4)	3
LDL-C 155 – 189 mg/dL (4.0–4.9)	1
DNA analysis	
Functional mutation in the *LDLR, apo B or PCSK9* gene	8
Diagnosis (diagnosis is based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6 – 8
Possible Familial Hypercholesterolemia	3 – 5
Unlikely Familial Hypercholesterolemia	<3

* Premature = < 55 years in men; < 60 years in women
LDL-C = low density lipoprotein cholesterol; FH, familial hypercholesterolemia.
LDLR = low density lipoprotein receptor
Apo B = apolipoprotein B
PCSK9 = Proprotein convertase subtilisin/kexin type 9

[1]Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *American journal of epidemiology.* 2004;160:407-420.

[2]Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Current opinion in lipidology.* 2012;23:282-289.

[3]Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *European heart journal.* 2013;34:3478-3490a.

APPENDIX C: SCHEDULE OF PROCEDURES

Table 6. Schedule of Procedures

Study Day Study Procedure	-7 to -28 Screen/V1	1 V2	15 (±3) V3	29 (±3) V4	43 (±3) V5	57 (±3) V6	71 (±3) V7	85 (±3) V8	99 (±3) V9	113/ET (±3) V10
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Prior/concomitant medications [1]	X	X	X	X	X	X	X	X	X	X
Physical examination	X [2]							X		X [3]
Weight	X [2]	X		X		X		X		X [2]
Height	X [2]									
Vital signs [4]	X	X	X	X	X	X	X	X	X	X
Full chemistry profile [5]	X [5a]	X		X		X		X		X
Brief chemistry profile [5]			X		X		X		X	
Hematology and urinalysis [5]	X	X		X		X		X		X
PK blood sample [6]		X	X	X	X	X	X	X	X	X
PCSK9 measurement [7]		X	X	X	X	X	X	X	X	X
Brief lipid panel only [5]	X		X		X		X		X	
Expanded lipid/apo panel [5]		X		X		X		X		X
Immunogenicity assessment		X		X		X		X		X [8]
Exploratory biomarkers [9]		X						X		X
12-lead ECG [10]	X							X		X [3]
Pregnancy/FSH test [11]	X									X
Randomization		X								
Study drug administration		X		X		X				
Injection site assessment		X [12]	X	X [12]	X	X [12]	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

See footnotes on next page.

All blood samples should be collected while the subject is in a fasted state (≥10 hours, water is allowed and encouraged) and PRIOR to completing other visit requirements other than weight

A ±3-day window is allowed for all clinic visits; unanticipated or unavoidable cancellations due to weather or public holidays may be scheduled within a 5-day window and will not be considered protocol deviation if appropriately documented.

1. To include lipid-lowering drugs. Current statin and dose and/or ezetimibe plus adherence at each visit.
2. A physical examination is required prior to study drug administration. If the screening visit physical examination was performed within 14 days of the randomization visit, it does not need to be repeated on Day 1. BMI calculated from weight and height.
3. Perform only if Early Termination.
4. Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the subject has been seated or supine for ≥5 minutes.
5. As outlined in Appendix D. [5a] TSH.
6. PK blood samples will be collected pre-dose.
7. Measurements will include total and unbound (free) PCSK9 and will be collected pre-dose.
8. Blood samples for immunogenicity assessment will be collected pre-dose. Subjects who test positive with safety related clinical sequelae may be asked to return for additional monthly follow-up testing. If positive NAbs at the final visit (week 16) patients to return for follow-up testing every 3 months until either NAbs are no longer detectable or the subject has been followed for a period of at least 12 months – see section 6.2.11
9. Exploratory biomarker blood samples will be collected and frozen for potential assessment of additional lipid or other biomarkers.
10. Subjects should be resting in the supine position for ≥10 minutes prior to each 12-lead ECG.
11. A serum pregnancy test will be performed only on women of childbearing potential. Serum FSH will be measured for women uncertain of post-menopausal status (<1 year since last menses).
12. On Days 1, 29, and 57, injection site assessments will be performed pre-dose and 15 minutes post-dose.

apo = apolipoprotein; ECG = electrocardiogram; ET = Early Termination; FSH = follicle-stimulating hormone; PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; SC = subcutaneous; TSH = thyroid-stimulating hormone.

APPENDIX D: CLINICAL LABORATORY ANALYTES

Full Safety Chemistry Panel (22 tests, 1 calculation)

- Alanine aminotransferase
- Albumin
- Alkaline phosphatase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Blood urea nitrogen
- Calcium
- Chloride
- Creatine kinase
- Creatinine
- Estimated glomerular filtration rate
- Gamma-glutamyl transferase
- Glucose
- Inorganic phosphorus
- Lipase
- Potassium
- Sodium
- Total bilirubin [1]
- Total protein
- Uric acid
- Total cholesterol
- Triglyceride

1. If total bilirubin levels increase by >1.1 mg/dL, direct and indirect bilirubin will also be measured. Subjects with mild unconjugated hyperbilirubinemia due to Gilbert's syndrome are not excluded

Brief Safety Chemistry Panel (10 tests 1 calculation)

- Alanine aminotransferase
- Alkaline phosphatase
- Aspartate aminotransferase
- Albumin
- Total bilirubin [1]
- Creatinine
- Creatine kinase
- Estimated glomerular filtration rate
- Glucose
- Total cholesterol
- Triglyceride

1. If total bilirubin levels increase by >1.1 mg/dL, direct and indirect bilirubin will also be measured.

Brief Fasting Lipid Panel

- HDL cholesterol (HDL-C)
- LDL-C [1]
- Non–HDL-C (TC minus HDL-C)

1. LDL-C will be calculated by Friedewald and Hopkins formulae.

Expanded Lipid panel

- Brief lipid panel as above
- LDL-C/VLDL-C by ultracentrifugation (BQuant)
- Apo A1, apo B, and Lp(a)

Endocrinology

Serum pregnancy test for women of childbearing potential
Serum follicle-stimulating hormone (FSH) for women uncertain of post-menopausal status (<1 year since last menses)
Thyroid-stimulating hormone (TSH) [1]

1. If TSH <LLN or >1.5 × ULN FT3 is performed.

Hematology

Hematocrit
Hemoglobin
Platelets
Red blood cell count
White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin
Blood
Glucose
Ketones
Leukocyte esterase
Microscopy [1]
Nitrite
pH
Protein
Specific gravity
Urobilinogen

1. Microscopy is performed only as needed based on positive dipstick test results.

Serum pregnancy test (for all women of childbearing potential)

Exploratory Biomarkers: Serum sample to be aliquoted and frozen at -70°C on arrival at the central laboratory