CLINICAL STUDY PROTOCOL

Open-Label Extension, Phase 2b Study to Evaluate the Longer Term Efficacy and Safety of LIB003 in Patients on Stable Lipid-Lowering Therapy Requiring Additional LDL-C Reduction

Investigational Product: LIB003
Protocol Number: LIB003-010
IND Number: 134579

Sponsor:
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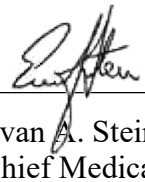
Date: 21 December 2018

SIGNATURE PAGE

STUDY TITLE: Open-Label Extension, Phase 2b Study to Evaluate the Longer Term 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
	March 18, 2020

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 patients.

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

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: Open-Label Extension, Phase 2b Study to Evaluate the Longer Term Efficacy and Safety of LIB003 in Patients on Stable Lipid-Lowering Therapy Requiring Additional LDL-C Reduction

PROTOCOL NUMBER: LIB003-010

INVESTIGATIONAL PRODUCT: LIB003

PHASE: 2b

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) without cardiovascular disease who need additional LDL-C reduction

OBJECTIVES:

The primary objectives of this study are to assess the longer term safety, tolerability, and LDL-C-lowering efficacy after 52 weeks of additional treatment with LIB003 at a subcutaneous (SC) dose of 300 mg every 4 weeks (Q4W). Study patients will be those with hypercholesterolemia on stable diet and oral LDL-C-lowering drug therapy who have completed the Phase 2 dose finding study.

The secondary objectives of this study are the following:

- To assess the longer term tolerability and safety of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the stability of LDL-C-lowering with LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the pharmacodynamic (PD) effect on serum unbound (free) proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects 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) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects on apolipoprotein (apo) B and lipoprotein (a) (Lp[a]) serum concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;

- To assess the pharmacokinetics of LIB003 and PCSK9 following multiple doses of LIB003 300 mg SC Q4W;
- To assess the frequency of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo, including those with detectable ADAs during the Phase 2 double-blind study; and
- Patients who develop neutralizing antibodies at Week 52 may be administered up to 3 additional doses of LIB003 300 mg QW4 for a total of up to 64 weeks exposure to allow for the assessment and characterization of this finding. Following the first dose, if NAbs continue positive with possible attenuation of free PCSK9 and LDL-C, then up to 2 additional doses could be administered.

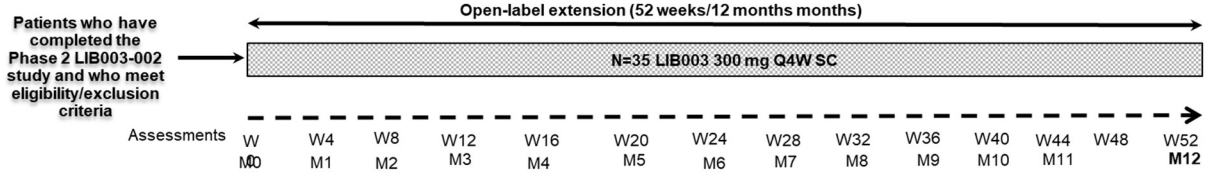
POPULATION:

The population for this study includes men and women who are ≥18 years of age who completed the double-blind, placebo-controlled 16-week Phase 2 study (LIB003-002) and will continue on stable lipid-lowering oral drug therapy (eg, tolerable statin with or without ezetimibe).

STUDY DESIGN AND DURATION:

This is an open-label, Phase 2b extension study of 52 weeks duration. Approximately 35 men and women aged ≥18 years who have completed the Phase 2 (LIB003-002) study and fulfill the inclusion and exclusion criteria will be enrolled at up to 4 sites in the United States. All patients will receive LIB003 at a dose of 300 mg administered SC Q4W.

LIB003-010 Phase 2b Study Design



M = month; Q4W = every 4 weeks; SC = subcutaneously; W = week.

Study Procedures

Patients who have completed the LIB003-002 study and do not meet any exclusion criteria and have completed the informed consent for this extension study will receive LIB003 at a dose of 300 mg Q4W by SC injection at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified visits during the study. All lipid measurements on Week 0/Month 0 onward will be available to the Investigator, patients, 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.

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

Patients who test positive for binding, non-NAbs and have clinical sequelae at Week 52/Early Termination 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 52/Early Termination), patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months. During the initial 3 months of follow-up patients may continue to receive LIB003 300mg at visits Q4W for a potential total exposure of 64 weeks to further characterize the NAb finding. Following the first dose, if NAbs continue positive with possible attenuation of free PCSK9 and LDL-C, then up to 2 additional doses could be administered.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

All patients will receive SC doses of LIB003 300 mg administered as a SC injection by clinic personnel.

PHARMACOKINETIC VARIABLES:

Total serum PCSK9 concentrations at Weeks 24 and 36 and 52/Early Termination will be assessed.

PHARMACODYNAMIC VARIABLES:

The PD parameters include changes from both baseline in the Phase 2 (LIB003-002) study and Week 0 in this study in LDL-C (calculated and measured), unbound (free) PCSK9 concentrations, serum lipid parameters (TC, HDL-C, non–HDL-C, VLDL-C, TG, apo B, 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 primary objectives of this study are to assess the percent change from baseline, from the original LIB003-002 study, in LDL-C level at Week 52 (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. Interim analyses will be carried out at Weeks 24 and 36 weeks. Results will be summarized descriptively.

Safety Analyses

The safety endpoint data will be summarized for the Safety Population, which is defined as all patients 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. 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 and preferred term.

The safety laboratory data will be summarized by visit, along with changes from baseline visit of the extension study. 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, along with the changes from baseline. Abnormal physical examination findings will be listed.

Immunogenicity data will be listed.

SAMPLE SIZE DETERMINATION:

The number of patients is not based on statistical consideration and there is no placebo or comparator group.

SITES: Four 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
CFR	Code of Federal Regulations
CK	Creatine kinase
CRA	Clinical Research Associate
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
Enrollment	The day patient signs informed consent and first procedure performed
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HSA	Human serum albumin
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
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
LOCF	Last post-baseline observation carried forward
Lp(a)	Lipoprotein (a)
mAb	Monoclonal antibody
NAb	Neutralizing antibody
OTC	Over-the-counter

Abbreviation	Definition
Pharmacy manual	Manual provided by the Sponsor or CRO containing detailed information on study drug (LIB003), receipt and storage, preparation (SC), and drug accountability
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
Q4W	Every 4 weeks
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous(ly)
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

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 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.

Phase 1 study:

LIB003 has been studied in a Phase 1 single ascending dose (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.

Safety: 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. Summary of Adverse Events for the LIB003-001 SAD Study

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

AE = adverse event; CNS = central nervous system; ISR = injection site reaction; IV = intravenous; PBO = placebo; Resp Infec = respiratory infection; SAD = single ascending dose; SC = subcutaenous(ly); TEAE = treatment-emergent adverse event. Source: LIB003-001 Clinical Study Report

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%) 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), central nervous system (headache), and musculoskeletal; all other adverse events were reported by 1 subject only. None appeared dose related or more frequently 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 administration. 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). The Benadryl was replaced with cetirizine 10 mg orally 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 creatine kinase (CK) that were clearly related to exercise or excessive or unusual physical activity, and CK decreased at subsequent testing.

There were no adverse events based on ECG findings or any findings that were assessed as clinically significant by the Investigator.

Anti-drug (anti-LIB003) antibodies (ADAs) were confirmed in 2 subjects: One subject treated with 25 mg SC of LIB003 developed low titer non-neutralizing ADAs at Day 43; the titers remained low on monthly follow-up, with a stable titer of 160 after 3 months. The second subject, treated with 600 mg IV of LIB003, developed an ADA response at Day 22, which increased to a titer of 2560 by Day 43. The patient was followed at weekly intervals until Day 57 when LDL-C returned to within 20% of baseline and was followed at monthly intervals for 2.5 months after Day 43, reaching a maximal titer of 5120 at Day 113, which declined 50% on Day 142. There were no associated clinical or laboratory adverse effects noted and there did not appear to be any neutralizing impact on efficacy as LDL-C and free PCSK9 reduction did not appear attenuated compared to other subjects treated with LIB003 in the same cohort. Evaluation in the LIB003 neutralizing antibody (NAb) assay indicated that these ADAs were neutralizing beginning on Day 29 through Day 113 and were no longer neutralizing on Day 142. At a routine clinic visit on 01 August 2018 (1 month after ending the study) to the Principal Investigator (PI), who was also the patient's lipid doctor, the patient reported a recent upper right lung lobe mass found by their primary care physician on 24 July 2018 and on biopsy taken 30 July 2018 diagnosed as Epstein-Barr positive diffuse large B cell lymphoma of intra thoracic lymph nodes. The finding was determined by the PI as unrelated to study drug.

Efficacy: Mean reductions in free PCSK9 were rapid with all doses and reached more than 99% within 12 hours and were sustained in virtually all subjects 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 patients on non-lipid-lowering subjects, it had decreased to 12% and in those on statins to 54% of baseline levels. The reduced effects in free PCSK9 were reflected in less reductions of LDL-C and apolipoprotein (apo) B in statin-treated subjects although greater reductions were maintained in subjects not on lipid-lowering therapy. However, the 150 mg 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, based on prior data from studies with mAbs, it is anticipated that multiple dosing will result in longer duration of both free PCSK9 suppression and LDL-C reduction. Furthermore, extensive prior data show 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. Three doses were selected for the Phase 2 study to be administered SC every 4 weeks (Q4W); 150 mg, 300 mg, and 350 mg.

Phase 2 study:

Based on the free PCSK9 and LDL-C data from the SAD study and an objective of obtaining maximal and stable LDL-C reductions with dosing at least Q4W in a volume that is consistent with a single SC injection via an autoinjector (≤1.5 mL), a 16-week Phase 2 study was done. This was a double-blind, placebo-controlled, dose-finding study in approximately 81 patients with ASCVD, or at high risk for ASCVD, or HeFH without cardiovascular disease, on stable maximal tolerable statin and/or ezetimibe which was completed on 09 November 2018. The doses assessed included 150 mg, 300 mg, and 350 mg all administered SC Q4W on Days 1, 29, and 57 with the final efficacy endpoint at Day 85 (Week 12). Patients were monitored for 4 additional weeks at Days 99 and 113. Patients were randomized within each treatment group to LIB003 or placebo in a ratio of 3:1 resulting in 20 patients on placebo and 61 patients in the LIB003 treatment groups (21 on 150 mg, 19 on 300 mg, and 21 on 350 mg). Of the 81 patients randomized, 79 completed the study; of the 2 patients not completing the study, 1 was terminated after 4 weeks after starting on a prescription PCSK9 monoclonal antibody while the second patient withdrew after receiving the first dose due to conflict with her work schedule.

Safety: There were no deaths and all 3 doses were safe and well tolerated (see Table 2). Serious adverse events occurred in 5.0% (1/20) subjects in the placebo group, 4.8% (1/21) in the LIB003 150 mg group, 10.5% (2/19) in the LIB003 300 mg, and 9.5% (2/21) in the LIB003 350 mg group. Of the entire 81 patients, 24 were found to have positive ADAs on screening, of which 19 were confirmed as positive. This included 2 patients (2.5%) who tested positive prior to receiving study drug and whom showed the highest titers (160 and 1280) and in both patients, titers decreased progressively after dosing with study drug. Excluding these 2 patients, ADAs were found to be present post-dose in 27.8% (17/61) patients treated with LIB003 and 0% (0/20) on placebo. All positive ADAs post-dosing of study drug had low, or below level of quantitation, levels and based on individual free PCSK9 and LDL-C levels, there did not appear to be a pharmacokinetic (PK)/pharmacodynamic (PD) effect. Subsequent testing was negative for treatment-induced NAbs.

Table 2. Overview of Adverse Events for the LIB003-002 Study

Treatment group	Placebo	LIB003 150 mg Q4W	LIB003 300 mg Q4W	LIB003 350 mg Q4W	Total
Number of patients	N=20	N=21	N=19	N=21	N=81
Subjects with any TEAE	10 (50.0)	9 (42.9)	11 (57.9)	13 (61.9)	43 (53.1)
Maximum severity of TEAE					
Mild	5 (25.0)	5 (23.8)	8 (42.1)	5 (23.8)	23 (28.4)
Moderate	4 (20.0)	3 (14.3)	2 (10.5)	5 (23.8)	14 (17.3)
Severe	1 (5.0)	1 (4.8)	1 (5.3)	3 (14.3)	6 (7.4)
Subjects with any study drug-related TEAE	2 (10.0)	1 (4.8)	1 (5.3)	2 (9.5)	6 (7.4)
Maximum severity of study drug-related TEAE					
Mild	1 (5.0)	1 (4.8)	1 (5.3)	2 (9.5)	5 (6.2)
Moderate	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any treatment-emergent SAE	1 (5.0)	1 (4.8)	2 (10.5)	2 (9.5)	6 (7.4)
Subjects with any study drug-related treatment-emergent SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with TEAE leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any study drug-related TEAE leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with any TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N = number of subjects; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: LIB003-002 Clinical Study Report

Efficacy: The co-primary endpoints of percent reduction in LDL-C (calculated by Friedewald formula) from baseline compared to placebo at Week 12 and the mean of Weeks 10 and 12 was achieved ($p<0.0001$) for all 3 doses (see Table 3); however, maximal and stable reductions were

best seen with the 300 mg dose [least-squares mean (standard error; 95% confidence interval) of -77.3% (6.63; -90.5, -64.1)] at Week 12 (last post-baseline observation carried forward [LOCF]) and -76.1% (4.99; -86.0, -66.2) at mean of Weeks 10 and 12 (LOCF). These results were consistent with LDL-C measured by Hopkins formula and by preparative ultracentrifugation. The lower dose of 150 mg, while achieving similar LDL-C reductions at 2 weeks post dose, was insufficient to provide consistent free PCSK9, and more importantly LDL-C, reductions for 4 weeks. The larger dose of 350 mg Q4W provided no additional LDL-C reduction at any time point.

Table 3. Analysis of Variance of Low-Density Lipoprotein Cholesterol (Calculated by Friedewald Formula) for the LIB003-002 Study

Visit Statistic	LIB003 150 mg (N = 21)	LIB003 300 mg (N = 19)	LIB003 350 mg (N = 20)
Average Weeks 10 and 12 LOCF			
LIB003 vs Placebo LS Mean (SE)	-48.0 (4.87)	-76.1 (4.99)	-70.3 (4.93)
95% CI	(-57.7, -38.3)	(-86.0, -66.2)	(-80.1, -60.5)
p-value	<0.0001	<0.0001	<0.0001
Week 12 LOCF			
LIB003 vs Placebo LS Mean (SE)	-33.5 (6.47)	-77.3 (6.63)	-70.1 (6.54)
95% CI	(-46.3, -20.6)	(-90.5, -64.1)	(-83.2, -57.1)
p-value	<0.0001	<0.0001	<0.0001

CI = confidence interval; LOCF = last post-baseline observation carried forward; LS = least squares; SE = standard error; N = number of subjects; vs = versus.
Source: LIB003-002 Clinical Study Report

Based on the results the dose of 300 mg (1.2 mL) SC Q4W was selected for the open-label extension (LIB003-010) study.

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

1.1 Rationale

The rationale for this extension study is to enable longer term assessment of the safety, tolerability, and LDL-C-lowering efficacy for a 52-week additional treatment with LIB003 at a SC dose of 300 mg Q4W. Study patients will be those with hypercholesterolemia on stable diet and oral LDL-C-lowering drug therapy who have completed the Phase 2 dose finding study.

Additional objectives of this study are the following:

- To assess the frequency of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo, including those with detectable ADAs during the Phase 2 double-blind study;
- To assess the longer term tolerability and safety of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the stability of LDL-C-lowering with LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;

- To assess the PD effect on serum unbound (free) PCSK9 concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects 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) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the PK of LIB003 and PCSK9 following multiple doses of LIB003 300 mg SC Q4W; and
- To assess the effects on apo B and lipoprotein (a) (Lp[a]) serum concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study.

In patients who are NAb positive at Week 52, the rationale for up to 3 additional doses of LIB003 300mg QW4 (12 additional weeks of exposure) is to allow for the assessment of the time course of NAbs and effects on relevant clinical and laboratory measures including but not limited to free PCSK9 and LDL-C.

The risk of continuing treatment for up to 12 additional weeks (64 weeks total exposure) is considered low. Currently, 3 of 112 (approximately 2.7%) patients who have received LIB003 to date have developed NAbs. No patient has had a concurrent change in their clinical or laboratory safety or efficacy findings. The PCSK9 free and LDL-C lowering effects remained consistent to previous visits when there were no NAbs detected, negating any indication of a neutralizing clinical effect. In 2 prior patients, NAbs were detected and then resolved while the patient remained on LIB003 treatment or followed after completing treatment in the phase 1 single ascending dose trial.

Safety, immunogenicity, and PD data derived from the study will further support the Phase 3 studies.

1.2 Risk/Benefit

Patients will receive no known clinical benefit from participating in the study beyond that of an assessment of their overall health status and reduction in LDL-C.

LIB003 at doses of 300 mg given were shown to reduce LDL-C levels >60% and was safe and well tolerated in the Phase 2 study these patients previously participated in. Therefore, the risk to patients in this study is considered low.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives of this study are to assess the longer term safety, tolerability, and LDL-C-lowering efficacy after 52 weeks of additional treatment with LIB003 at a SC dose of 300 mg Q4W. Study patients will be those with hypercholesterolemia on stable diet and oral LDL-C-lowering drug therapy who have completed the Phase 2 dose finding study.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

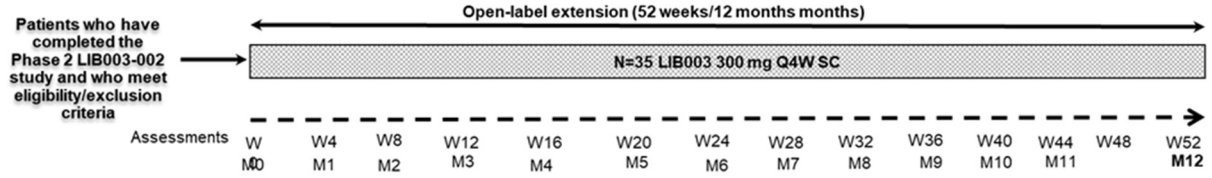
- To assess the longer term tolerability and safety of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the stability of LDL-C-lowering with LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the PD effect on serum unbound (free) PCSK9 concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects on serum lipids, including TC, HDL-C, non–HDL-C, VLDL-C, and TG of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects on apo B and Lp(a) serum concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the PK of LIB003 and PCSK9 following multiple doses of LIB003 300 mg SC Q4W; and
- To assess the frequency of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo, including those with detectable ADAs during the Phase 2 double-blind study.
- Patients who develop NAbs at Week 52 may be administered up to 3 additional doses of LIB003 300 mg QW4 for a total of up to 64 weeks exposure to allow for the assessment and characterization of this finding. Following the first dose, if NAbs continue positive with possible attenuation of free PCSK9 and LDL-C, then up to 2 additional doses could be administered.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is an open-label, Phase 2b extension study of 52 weeks duration. Approximately 35 men and women aged ≥18 years who have completed the Phase 2 (LIB003-002) study and fulfill the inclusion and exclusion criteria will be enrolled at up to 4 sites in the United States. All patients will receive LIB003 at a dose of 300 mg administered SC Q4W as shown in Figure 1.

Figure 1. LIB003 Phase 2b Open-Label Extension Study



M = month; Q4W = every 4 weeks; SC = subcutaneously; W = week.

Patients who have completed the LIB003-002 study and do not meet any exclusion criteria and have completed the informed consent for this extension study will receive LIB003 at a dose of 300 mg Q4W by SC injection at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified visits during the study. All lipid measurements on Week 0/Month 0 onward will be available to the Investigator, patients, 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 assessed at each visit.

Patients testing positive for ADAs will be tested for NAbs and titer, and may be further characterized for isotype, binding site, affinity, and presence of immune complexes.

Patients who test positive for binding, non-NAbs and have clinical sequelae at Week 52/Early Termination 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 52/Early Termination), patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months. During the initial 3 months of follow-up patients may continue to receive LIB003 300mg at visits Q4W for a potential total exposure of 64 weeks to further characterize the NAb finding. Following the first dose, if NAbs continue positive with possible attenuation of free PCSK9 and LDL-C, then up to 2 additional doses could be administered.

3.2 Stopping Rules

Dose-Limiting Toxicity

Dosing of a patient 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 patients 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; or
- ≥2 patients have AST and/or ALT >5 × ULN (confirmed by repeat).

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Successful completion of the double-blind, placebo-controlled Phase 2 (LIB003-002) study without serious adverse events related to LIB003;
2. Provision of written and signed informed consent (by patient) prior to any study-specific procedure;
3. Women of childbearing potential must be using an effective form of birth control[#] and have a negative pregnancy test at Week 0. Effective contraception must be maintained during the entire time of taking the study drug and for 90 days after the last dose of study drug. ;
4. Willing to maintain appropriate diet and stable dose of current statin (if tolerable) and/or ezetimibe for the duration of the 52-week study;
5. Male patients will either be surgically sterile or agree to use, from the time study drug is started until 90 days following the last dose of study drug, one of the following forms of contraception: male or female condom with spermicide; a female partner who is surgically sterile, post-menopausal or who agrees to use effective contraception the following contraceptives, diaphragm or cervical cap with spermicide; or intrauterine device (IUD), oral, implantable, or injectable contraceptives;
6. Male patients must refrain from sperm donation until 90 days following the last dose of study drug; and
7. Patient is considered by the Investigator to be otherwise healthy, based on medical history review, a defined complete physical examination, as well as vital sign measurements, ECGs, and laboratory test results.

[#] *Effective methods of birth control include abstinence, birth control pills or patches, intrauterine devices (IUDs), sexual activity with a male partner who has had a vasectomy, condom or diaphragm or cervical cap with spermicide or IUD, oral, implantable, or injectable contraceptives.*

4.2 Exclusion Criteria

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

1. Failure to complete the Phase 2 (LIB003-002) study or and serious adverse event (SAE) related to study drug;
2. Development since the final visit in LIB003-002 of any *concomitant clinical condition* or *acute and/or unstable systemic* disease compromising patient 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 patient safety consideration or could interfere with the results of the study;
3. Females of childbearing potential not using or willing to use an effective form of contraception[#], or pregnant or breastfeeding, or who have a positive urine pregnancy test at Week 0;
4. Planned cardiac surgery or revascularization;
5. New York Heart Association II-IV heart failure;
6. Patient is currently, or within the prior 2 weeks has taken PCSK9 mAbs or within the last 6 months PCSK9 small interfering ribonucleic acid or locked nucleic acid-reducing agents;
7. 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);
8. Patient will not be available for protocol-required study visits or procedures, to the best of the patient's and Investigator's knowledge;
9. Has any other finding which, in the opinion of the Investigator, would compromise the patient's safety or participation in the study; or
10. Is an employee or family member of the Investigator or study site personnel.

[#] *Effective methods of birth control include abstinence, birth control pills or patches, intrauterine devices (IUDs), sexual activity with a male partner who has had a vasectomy, condom or diaphragm or cervical cap with spermicide or IUD, oral, implantable, or injectable contraceptives.*

4.3 Withdrawal Criteria

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

- The patient withdraws consent or requests discontinuation from the study, or study drug, for any reason;
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol;
- Any 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 patient;

- Pregnancy;
- Requirement of prohibited concomitant medication as outlined above;
- Patient failure to comply with protocol requirements or study-related procedures which results, or could result, in significant increased risk to the patient; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient 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 at Week 52. The reason for patient withdrawal must be documented in the electronic Case Report Form (eCRF).

Withdrawn patients may not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Group

All patients will receive SC LIB003 at a dose of 300 mg Q4W.

5.2 Rationale for Dosing

In the previous Phase 2 study (LIB003-002), the 300 mg SC dose QW4 was safe and well tolerated and provided maximal and stable reduction in mean LDL-C for 4 weeks.

5.3 Randomization and Blinding

This is an open-label extension study, therefore, no randomization or blinding is necessary.

5.4 Breaking the Blind

This is an open-label extension study, therefore, no blinding is necessary.

5.5 Drug Supplies

5.5.1 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.

5.5.2 Study Drug Preparation and Dispensing

LIB003 should be withdrawn directly from the vial into a suitable size syringe for injection. Solutions of LIB003 may foam; therefore, shaking and excessive agitation of vials should be avoided, or if performed, sufficient time allowed for the contents to settle prior to withdrawing the contents. Additionally, care must be taken to ensure the sterility of the prepared solution, as the drug product does not contain antimicrobial preservatives or bacteriostatic agents. To assure sterility of the prepared solutions, the vials are for single use only.

Trained medical personnel will administer LIB003 to patients 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.

5.5.3 Study Drug Administration

Study drug (LIB003 300 mg) will be administered by SC injection on Week 0 and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Study drug will be administered under the supervision of the site personnel.

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

5.5.4 Treatment Compliance

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

5.5.5 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 pharmacist or trained nurse 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 patient will be kept on a study drug accountability log.

Study drug accountability records will be maintained by the pharmacist or designated qualified and trained site staff in a secure location. Drug accountability records will be available for verification by LIB Therapeutics 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 patient 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 patient that should not be delayed. All therapy and/or medication administered to manage adverse events should be recorded in the appropriate eCRF.

Any other investigational drug taken within 30 days or 5 half-lives (whichever is longer) prior to Week 0 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 PCSK9 drugs.

5.6.3 Restrictions and Dietary Guidelines

Patients 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.

Patients 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. Patients 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. Patients 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 patients before any protocol-specific procedures are performed. The Investigator must ensure that patients, or, in those situations where consent cannot be given by patients, 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 ±5-day window is allowed for all clinic visits; unanticipated or unavoidable cancellations due to weather or public holidays may be scheduled within a 7-day window and will not be considered protocol deviations if appropriately documented.

All blood and urinalysis samples should be collected while the patient is in a fasted state (≥10 hours; ad libitum water is allowed and encouraged) and prior to administration of LIB003.

6.2.1 Study Week 0

The following procedures will be performed at Week 0:

- Obtain informed consent;
- Evaluate inclusion/exclusion criteria;
- Update medical history;
- Perform urine pregnancy test at clinical site (only women of childbearing potential);
- Record prior and concomitant medications, including statin, statin dose, and/or ezetimibe plus adherence since last visit of LIB003-002 study;
- Perform physical examination;
- Measure weight and calculate body mass index;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect fasting urine sample pre-dose for urinalysis;
- Collect fasting blood samples pre-dose for the following:
    - Full safety chemistry and hematology panels and thyroid-stimulating hormone;
    - Expanded lipid panel;
    - PCSK9; and
    - Immunogenicity;
- Administer SC dose of study drug;

- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.2 Study Week 4

The following procedures will be performed at Week 4:

- 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 fasting blood samples pre-dose for the following:
  - Brief safety chemistry panel;
  - Brief lipid panel;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;
- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.3 Study Week 8

The following procedures will be performed at Week 8:

- 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 fasting blood samples pre-dose for the following:
  - Brief safety chemistry panel;
  - Brief lipid panel;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;
- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.4 Study Week 12

The following procedures will be performed at Week 12:

- 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 fasting urine sample pre-dose for urinalysis;
- Collect fasting blood samples pre-dose for the following:
  - Full safety chemistry and hematology panels;
  - Expanded lipid panel;
  - PK;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;
- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.5 Study Weeks 16 and 20

The following procedures will be performed at Weeks 16 and 20:

- 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 fasting blood samples pre-dose for the following:
  - Brief safety chemistry panel;
  - Brief lipid panel;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;

- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.6 Study Week 24

The following procedures will be performed at Week 24:

- 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 fasting urine sample pre-dose for urinalysis;
- Collect fasting blood samples pre-dose for the following:
  - Full safety chemistry and hematology panels;
  - Expanded lipid panel;
  - PK;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;
- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.7 Study Weeks 28 and 32

The following procedures will be performed at Weeks 28 and 32:

- 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 fasting blood samples pre-dose for the following:
  - Brief safety chemistry panel;
  - Brief lipid panel;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;

- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.8 Study Week 36

The following procedures will be performed at Week 36:

- 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 fasting urine sample pre-dose for urinalysis;
- Collect fasting blood samples pre-dose for the following:
  - Full safety chemistry and hematology panels;
  - Expanded lipid panel;
  - PK;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;
- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.9 Study Weeks 40, 44, and 48

The following procedures will be performed at Weeks 40, 44, and 48:

- 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 fasting blood samples pre-dose for the following:
  - Brief safety chemistry panel;
  - Brief lipid panel;
  - PCSK9; and
  - Immunogenicity;
- Administer SC dose of study drug;
- Assess injection site pre-dose and 15 minutes post-dose; and
- Assess adverse events.

6.2.10 Study Week 52/Early Termination

The following procedures will be performed at Week 52/Early Termination:

- Record prior and concomitant medications, including statin, statin dose, and/or ezetimibe plus adherence for prior month;
- Perform urine pregnancy test at clinical site (only women of childbearing potential);
- Perform physical examination;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect fasting urine sample for urinalysis;
- Collect fasting blood samples for the following:
  - Full safety chemistry and hematology panels and thyroid-stimulating hormone;
  - Expanded lipid panel;
  - PK;
  - PCSK9; and
  - Immunogenicity;
- Assess injection site; and
- Assess adverse events.

6.2.11 Follow-up Visit for Positive Anti-Drug Antibodies/Neutralizing Antibodies

Patients who test positive for binding, non-NAbs and have clinical sequelae at Week 52/Early Termination that are considered safety related may be asked to return for additional monthly follow-up testing.

Patients with positive NAbs at the final visit (Week 52/Early Termination) will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months. During the initial 3 months of follow-up patients may continue to receive LIB003 300mg at visits Q4W for a potential total exposure of 64 weeks to further characterize the NAb finding.

The following procedures will be performed at the Follow-up Visit(s):

- 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 fasting urine sample for urinalysis;
- Collect fasting blood samples for the following:

  - Full safety chemistry and hematology panels;
  - Brief lipid panel;
  - PCSK9; and
  - Immunogenicity;
- Assess injection site; and
- Assess adverse events.

In addition to the procedures outlined above, the following procedures are to be conducted only in those patients with positive NAbs at Week 52 who continue up to 12 additional weeks (3 additional doses Q4W). Following the first dose, if NAbs continue positive with possible attenuation of free PCSK9 and LDL-C, then up to 2 additional doses could be administered.

- Urine pregnancy, physical examination and ECG will be assessed only at the last visit.
- LIB003 will be administered at every Q4W visit.

7 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

All blood samples should be collected while the patient is in a fasted state (≥10 hours ad libitum water is allowed and encouraged) and prior to administration of LIB003. 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 Pharmacodynamic Endpoints

The percent change from baseline in LIB003-002 study in LDL-C level at Weeks 36 and 52 (by Friedewald and Hopkins formula and ultracentrifugation/BQuant).

The PD parameters include changes from both baseline in the Phase 2 (LIB003-002) study and Week 0 in this study in LDL-C (calculated and measured), unbound (free) PCSK9 concentrations, serum lipid parameters (TC, HDL-C, non-HDL-C, VLDL-C, TG, apo B, and Lp[a]).

Baseline is defined as Day 1 of the Phase 2 dose-finding trial.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient 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 following the first dose of study drug until study participation is complete. Patients should be instructed to report any adverse event that they experience to the Investigator. From the time following the first dose of study drug, 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 the time of the first dose of study drug should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in nature 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 the time of the first dose of study drug 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. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality,
- If action taken with the study drug is required as a result of the abnormality, or
- Based on the clinical judgment of the Investigator.

8.1.1 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).

8.1.2 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 patient may have.
- Concomitant drug – The other drugs the patient is taking or the treatment the patient 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.

8.1.3 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 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 patient 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 1 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 or elective treatment of a pre-existing condition that did not worsen from baseline. 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 patient 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.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until the end of study visit (Week 36/Early Termination) or the Follow-up Visit or 30 days after the last administration of study drug if the patient does not complete the study 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.

Any SAE, regardless of expectedness or causality, should be reported by completing the adverse event eCRF form (when Serious = Yes) electronically in the Electronic Data Capture (EDC) system. When the form is completed, Medpace Clinical Safety will be notified electronically. If the event meets serious criteria and it is not possible to access the EDC system, e-mail or fax a completed paper back up-SAE form to the Medpace Clinical Safety contacts listed below within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered into EDC within 24 hours of the system becoming available. Any supporting documentation (eg, patient discharge summary, hospital records, autopsy reports, etc) should be submitted to Medpace Clinical Safety via e-mail or fax.

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 the patient(s) until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If the patient or partner of a patient 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 patient becoming pregnant while on study drug will immediately be withdrawn from the study and Early Termination study procedures will be performed.

The patient 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.

8.5 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 Food and Drug Administration (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.

8.6 Clinical Laboratory Evaluations

Clinical laboratory panels for lipids, hematology, serum chemistry, and urinalysis will be evaluated from samples collected after ≥10 hours of fasting (ad libitum water is allowed and encouraged) and prior to administration of LIB003 at the time points specified in Table 4 (Appendix A).

A urine pregnancy test will be performed by the clinical site at Week 0 and the end of study visit (Week 52/Early Termination) only on women of childbearing potential.

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

8.6.1 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;
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.

8.7 Immunogenicity

Patients will be assessed for ADAs at designated study visits specified in Table 4 (Appendix A). Patients testing positive for LIB003 antibodies will be tested for NAbs and titer, and may be further characterized for isotype, binding site, affinity, and presence of immune complexes.

Patients who test positive for binding, non-NAbs and have clinical sequelae at Week 52/Early Termination 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 52/Early Termination) patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months. During the initial 3 months of follow-up patients may continue to receive LIB003 300mg Q4W for a potential total exposure of 64 weeks to further characterize the NAb response.

8.8 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at designated study visits specified in Table 4 (Appendix A). Blood pressure and heart rate will be measured after the patient has been seated or supine for ≥5 minutes.

8.9 Electrocardiograms

Twelve-lead (single) ECGs will be assessed at designated study visits specified in Table 4 (Appendix A). Patients should be resting in the supine position for ≥10 minutes prior to each 12-lead ECG.

8.10 Physical Examinations

A full physical examination will be performed at the time points specified in Table 4 (Appendix A). Injection site reactions will be monitored by examination of injection site at the time points specified in Table 4 (Appendix A).

9 STATISTICS

9.1 Statistical Methods

9.1.1 Analysis Populations

The Intent-to-Treat (ITT) Population is defined as all patients who entered the open-label extension study.

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

9.1.2 Analysis of Efficacy

The primary objectives of this study are to assess the percent change from baseline, from the original LIB003-002 study, in LDL-C level at Week 52 (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. Results will be summarized descriptively.

Baseline is defined as Day 1 of the Phase 2 dose-finding trial.

9.1.3 Pharmacodynamic Analysis

Pharmacodynamic analysis will be performed based on the ITT Population. Total and unbound (free) serum PCSK9 concentrations at Weeks 24 and 36 and 52/Early Termination will be assessed. Pharmacodynamic endpoints will be summarized descriptively at each visit.

9.1.4 Immunogenicity Analyses

Immunogenicity data will be listed. Anti-drug antibodieswill be measured at Weeks 0, 12, 24, 36 and 52. Patients who develop positive ADAs will have additional measurements at visits after the last negative measurement

9.1.5 Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed based on the ITT Population. All PK parameters and PK concentrations will be summarized descriptively.

9.1.6 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. 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 and preferred term and reviewed for potential significance and clinical importance.

The safety laboratory data will be summarized by visit, along with changes from baseline visit of the extension study. 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, along with the changes from baseline. Abnormal physical examination findings will be listed.

Immunogenicity data will be listed.

9.1.7 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

9.1.8 Interim Analysis

No interim analysis is planned for this study.

9.2 Sample Size Determination

The number of patients is not based on statistical consideration and there is no placebo or comparator group.

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 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 patients, 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 well-being 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 patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form (ICF), advertisements (if applicable), written information given to the patients, 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 patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient'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 patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient 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 patient.

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 patient 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. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient 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 patients (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 patient 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

LIB Therapeutics, LLC
5375 Medpace Way
Cincinnati, OH 45227
Telephone: 978-770-8443

12.2.2 Contract Research Organization

Medpace, Inc.
5375 Medpace Way
Cincinnati, OH 45227
Telephone: 513-579-9911
Fax: 513-579-0444

12.2.3 Drug Safety

Medpace Clinical Safety
5375 Medpace Way
Cincinnati, OH 45227
Telephone: 800-730-5779, dial 3 or 513-579-9911, dial 3
Fax: 866-336-5320 or 513-579-0444
Email: medpace-safetynotification@medpace.com

12.2.4 Biological Specimens

Medpace Reference Laboratories
5365 Medpace Way
Cincinnati, OH 45227
Telephone: 800-749-1737 or 513-336-3270
Fax: 513-336-3261

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 4. Schedule of Procedures

Study Week / Study Procedure	0	4	8	12	16 and 20	24	28 and 32	36	40, 44 and 48	52/ET	Follow-up Visit [12]
Informed consent	X										
Inclusion/exclusion criteria	X										
Medical history	X										
Urine pregnancy/test [1]	X									X	X[16]
Prior/concomitant medications [2]	X	X	X	X	X	X	X	X	X	X	X
Physical examination [3]	X									X	X[16]
Body weight	X [4]	X	X	X	X	X	X	X	X	X	X
Vital signs [5]	X	X	X	X	X	X	X	X	X	X	X
Full safety chemistry and hematology panel [6]	X			X		X		X		X	X
Thyroid-stimulating hormone [7]	X									X	
Brief safety chemistry panel [8]		X	X		X		X		X		
Urinalysis	X			X		X		X		X	X
PK blood sample				X		X		X		X	
PCSK9 measurement [9]	X	X	X	X	X	X	X	X	X	X	X
Expanded lipid/apo panel [10]	X			X		X		X		X	
Brief lipid panel only [11]		X	X		X		X		X		X
Immunogenicity assessment [12]	**X**	X	X	**X**	X	**X**	X	**X**	X	**X** [12]	X
12-lead ECG [13]	X									X	X[16]
Study drug administration [14]	X	X	X	X	X	X	X	X	X		X[16]
Injection site assessment [15]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

See footnotes on next page.

All blood and urinalysis samples should be collected while the patient is in a fasted state (≥10 hours, ad libitum water is allowed and encouraged) and ***prior to administration of study drug (LIB003).***

A ±5-day window is allowed for all clinic visits; unanticipated or unavoidable cancellations due to weather or public holidays may be scheduled within a 7-day window and will not be considered protocol deviations if appropriately documented.

1. A urine pregnancy test will be performed by the clinical site at Week 0 and Week 52/ET only on women of childbearing potential.
2. To include current statin, statin dose, and/or ezetimibe plus adherence at each visit.
3. Injection site reactions will be monitored by physical examination.
4. Body mass index will be calculated from body weight and height.
5. Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the patient has been seated or supine for ≥5 minutes.
6. A full chemistry and hematology panel as listed in Appendix B.
7. Thyroid-stimulating hormone will be tested at Weeks 0 and 52/ET only.
8. A brief chemistry panel as listed in Appendix B.
9. Samples will be collected at Weeks 0, 4, 8, 12, 16, 20, 28, 32, 40, 44, 48 and 52 for potential measurements of total and unbound (free) PCSK9. Total and unbound (free) PCSK9 will initially be measured at Weeks 12, 24, 36, and 52/ET and at additional visits where NAbs are detected.
10. An expanded lipid panel as listed in Appendix B.
11. A brief lipid panel as listed in Appendix B.
12. Samples will be collected at all visits with ADAs measured initially at Weeks 0, 12, 24, 36 and 52. Patients who develop positive ADAs will have additional measurements at visits after the last negative measurement. Patients who test positive for binding non-NAbs and have clinical sequelae that are considered safety-related at the final visit (Week 52/ET) may be asked to return for additional monthly follow-up testing. If positive NAbs are detected at the final visit (Week 52/ET), patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months.
13. Patients should be resting in the supine position for ≥10 minutes prior to each 12-lead ECG.
14. Study drug (LIB003) will be administered at a SC dose of 300 mg.
15. Injection site assessments will be performed pre-dose and 15 minutes post-dose.
16. To be conducted only in those patients with positive NAbs at Week 52 who continue up to 12 additional weeks (3 additional doses Q4W). Following the first dose, if NAbs continue positive with possible attenuation of free PCSK9 and LDL-C, then up to 2 additional doses could be administered. Urine pregnancy, physical examination and ECG will be assessed only at the last visit. LIB003 will be administered at every Q4W visit.

apo = apolipoprotein; ECG = electrocardiogram; ET = Early Termination; NAb = neutralizing antibody; PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; SC = subcutaneous.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Full Safety Chemistry Panel (19 tests, 1 calculation)

Alanine transaminase	Albumin
Alkaline phosphatase	Aspartate transaminase
Bicarbonate	Blood urea nitrogen
Calcium	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate	Glucose
Inorganic phosphorus	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. Patients with mild unconjugated hyperbilirubinemia due to Gilbert's syndrome are not excluded.

Brief Safety Chemistry Panel (10 tests, 1 calculation)

Alanine transaminase	Alkaline phosphatase
Aspartate transaminase	Albumin
Creatinine	Creatine kinase
Estimated glomerular filtration rate	Glucose
Total bilirubin [1]	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

High-density lipoprotein cholesterol (HDL-C)
Low-density lipoprotein cholesterol (LDL-C) [1]
Non–HDL-C (Total cholesterol minus HDL-C)

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

Expanded Fasting Lipid Panel

Brief lipid panel (above)
LDL-C/very low-density lipoprotein cholesterol by ultracentrifugation (BQuant)
Apolipoprotein B and lipoprotein (a)

Endocrinology

Urine pregnancy test for women of childbearing potential – performed at clinical site
Thyroid-stimulating hormone (TSH) [1]

1. If TSH < lower limit of normal or >1.5 × upper limit of normal, free triiodothyronine will be 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.