

CLINICAL STUDY PROTOCOL

Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Long-Term Efficacy and Safety of LIB003 in Heterozygous Familial Hypercholesterolemia Patients on Stable Lipid-Lowering Therapy Requiring Additional Low-Density Lipoprotein Cholesterol Reduction (LIBerate-HeFH)

Investigational Product: LIB003

Proposed INN: lerodalcibep

Protocol Number: LIB003-004

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Sponsor:

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SIGNATURE PAGE

STUDY TITLE: Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Long-Term Efficacy and Safety of LIB003 in Heterozygous Familial Hypercholesterolemia Patients on Stable Lipid-Lowering Therapy Requiring Additional Low-Density Lipoprotein Cholesterol Reduction (LIBerate-HeFH)

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

Signature

Date



October 21st 2020

David Kallend, MBBS
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: Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Long-Term Efficacy and Safety of LIB003 in Heterozygous Familial Hypercholesterolemia Patients on Stable Lipid-Lowering Therapy Requiring Additional Low-Density Lipoprotein Cholesterol Reduction (LIBerate-HeFH)

PROTOCOL NUMBER: LIB003-004

INVESTIGATIONAL PRODUCT: LIB003

PHASE: 3

INDICATION: Low-density lipoprotein cholesterol (LDL-C) reduction in patients with atherosclerotic cardiovascular (CV) disease (ASCVD), high risk of ASCVD, homozygous familial hypercholesterolemia (HoFH), or heterozygous familial hypercholesterolemia (HeFH) without CV disease (CVD) who require additional LDL-C reduction

OBJECTIVES:

The coprimary objectives of this study are to assess LDL-C reductions at Week 24 and the mean of Weeks 22 and 24 (calculated by Friedewald formula) with monthly (Q4W[≤ 31 days]) dosing of LIB003 300 mg administered subcutaneously (SC) compared to placebo in patients with HeFH on stable diet and maximally tolerated oral LDL-C lowering drug therapy.

The secondary objectives of this study will be assessed similarly to the coprimary objectives:

- To re-assess the LDL-C lowering effects with LDL-C calculated by Hopkins formula or preparative ultracentrifugation;
 - To assess safety and tolerability of LIB003 in HeFH;
 - To assess the pharmacodynamic (PD) effects of 300 mg LIB003 Q4W (≤ 31 days) on serum unbound (free) proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations;
 - To assess the effects of LIB003 on serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TG);
 - To assess the effects of LIB003 on apolipoprotein (apo) B and lipoprotein (a) (Lp[a]) serum concentrations;
 - To assess the pharmacokinetics (PK) of LIB003 and total PCSK9 following 300 mg Q4W (≤ 31 days) SC doses of LIB003;
 - To assess the frequency and level of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) following multiple SC doses of LIB003; and
 - To assess percentage of patients achieving current European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines.
-

The exploratory objectives of this study will be assessed similarly to the coprimary objectives:

- To assess the LDL-C response based on underlying genetic variants associated with HeFH; and
- To assess the effects on other lipid and CV risk biomarkers as appropriate.

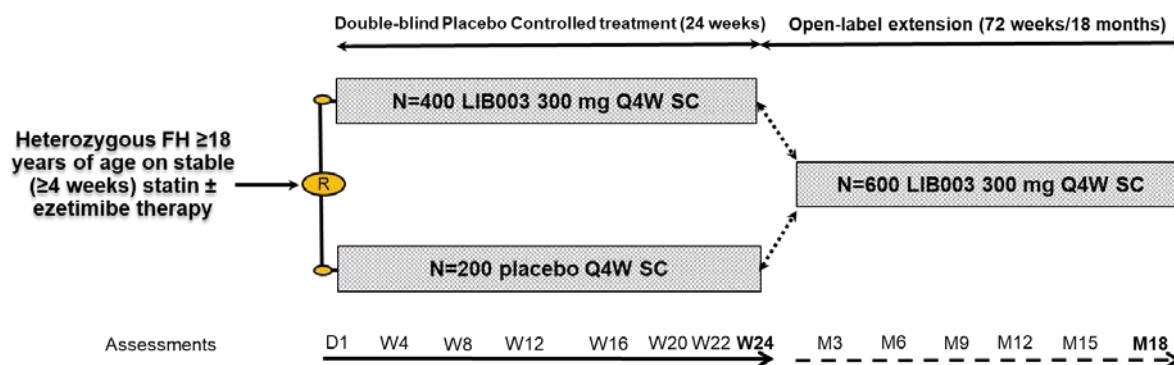
POPULATION:

The population for this study includes males and females who are ≥ 18 years of age with definite, probable or possible HeFH based either on clinical criteria (Simon Broome register criteria or Dutch Lipid Clinic Network Criteria) or genotyping and a calculated LDL-C (Friedewald) ≥ 70 mg/dL (if very-high risk for CVD) or ≥ 100 mg/dL (if high risk for CVD) and TG ≤ 400 mg/dL while on stable lipid lowering oral drug therapy (eg, maximally tolerated statin with or without ezetimibe). Patients unable to tolerate approved doses of a statin may take lower than approved doses and less frequently than daily as long as the dose and dosing frequency is consistent. Patients with documented intolerance to statins may also participate.

STUDY DESIGN AND DURATION:

This is a randomized, double-blind, placebo-controlled, Phase 3 study with LIB003 300 mg SC Q4W (≤ 31 days) of 24 weeks duration. Approximately 600 males and females aged ≥ 18 years who fulfill the inclusion and exclusion criteria will be enrolled at up to 60 sites in the United States, Canada, Central and South America, Europe, South Africa, Asia, Australasia, and the Middle East. Patients will be randomized in a 2:1 ratio to LIB003 (400 patients) or placebo (200 patients) administered SC Q4W (≤ 31 days). The study will consist of a Screening Period and a Treatment Period. The total study duration will be up to 35 weeks which includes up to an 11-week Screening Period (which may include up to an 8-week washout) and 24 weeks of study drug treatment.

LIB003-004 Phase 3 Study Design: Heterozygous Familial Hypercholesterolemia Study



D = day; FH = familial hypercholesterolemia; M = month; Q4W (≤ 31 days) = monthly; SC = subcutaneously; W = week.

Following randomization and dosing on Day 1, patients will be seen in the clinic Q4W (≤ 31 days) for 20 weeks and then at 2-week intervals for Weeks 22 and 24. All patients will receive doses of LIB003 300 mg Q4W (≤ 31 days) or placebo on Day 1 and Weeks 4, 8, 12, 16, and 20. In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified visits during the study. An aliquot of the lipid specimen at Day 1 and Week 24/ET will be stored for later analysis of exploratory lipid and CV risk biomarkers. A deoxyribonucleic acid sample will be obtained at Day 1 and will be analyzed, if necessary, for genetic confirmation and assessment of variants known to cause HeFH. All lipid, PK, and PCSK9 results from the baseline measurements following Day 1 will be blinded to the Investigator and all site and Sponsor personnel involved in the study. Final safety assessments will include adverse events and the results from physical examinations, electrocardiograms (ECGs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. Injection site reactions (ISRs) will be assessed at each visit drug is administered. Blinded safety, ISR, and lipid data will be reviewed by a Data Safety Monitoring Board (DSMB) at pre-determined intervals throughout the program. If indicated by these assessments, ADAs will be analyzed during study conduct to support safety monitoring. Patients with confirmed positive ADAs titers will have neutralizing antibodies (NAbs), PK (LIB003), and free PCSK9 assessed and may be further characterized for isotype, binding site, and affinity.

Patients completing the base study (LIB003-004) will be eligible to enter an open-label extension (OLE) study under a separate protocol and informed consent, where they will receive LIB003 300 mg Q4W (≤ 31 days) for an additional 72 weeks.

Patients on LIB003 who test positive for binding, non-NAbs and have clinical sequelae that are considered safety-related at the final visit of this study (Week 24 or Early Termination [ET]) may be asked to return for additional Q4W (≤ 31 days) follow-up testing if they terminate the base study (LIB003-004) and do not enter the OLE study.

Patients on LIB003 who test positive for NAbs at the final visit of this study (Week 24/ET), who do not enter the OLE study and who have no clinical sequelae, will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable, considered stable or the patient has been followed for a period of at least 12 months. For patients who test positive, but have not received active drug, follow-up testing will not be required.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The LIB003 drug product is a 250 mg/mL solution packaged in 1.2 mL volumes in a 2 mL clear glass vial with a stopper and aluminum crimp seal for a single SC injection of 300 mg.

All doses of LIB003 or placebo will be prepared by unblinded pharmacists and administered as a SC injection by unblinded clinic personnel who will not participate further in the evaluation of patients.

PHARMACODYNAMIC ASSESSMENTS:

LDL-C (calculated by Friedewald and Hopkins formulas, and measured by preparative ultracentrifugation), unbound (free) PCSK9 concentrations, TC, HDL-C, non-HDL-C, VLDL-C, TG, apo B, and Lp(a) will be measured.

PHARMACOKINETIC ASSESSMENTS:

The PK concentration for LIB003 will be measured.

SAFETY ASSESSMENTS:

Safety assessments will be AEs, including CV events (CVE), and all-cause mortality, the results of vital sign measurements, 12-lead ECGs, monitoring of ISRs, physical examinations, clinical laboratory tests, and immunogenicity evaluations.

In addition to ongoing safety monitoring by the Medical Monitor and clinical staff, a formally constituted and chartered DSMB will monitor safety, including all-cause mortality, CVEs, and immunogenicity (ADAs, NABs and any related clinical and PD effects) over the course of the study. The CVEs will be adjudicated by a blinded independent committee at an academic institution and provided to the DSMB on a regular basis.

STATISTICAL ANALYSES:

Efficacy Analysis

The coprimary efficacy endpoints are to assess percent change from baseline compared to placebo in LDL-C level (by Friedewald formula) at Week 24 and LDL-C level (by Friedewald formula) at the mean of Weeks 22 and 24. Percent change from baseline in LDL-C will be analyzed with analysis of covariance model with treatment as a factor and baseline value as a covariate. For patients in the Intent-to-Treat (ITT) Population who withdraw early, a multiple imputation will be used to explore the potential impact of missing data. For analysis of each primary objective, the treatment comparison will use a significance level of 0.05. Other efficacy variables will be analyzed similarly.

Pharmacodynamic Analysis

Pharmacodynamic analysis will be performed based on the ITT Population, which is defined as all patients who are eligible and randomized into the study. Pharmacodynamic and exploratory endpoints will be summarized at each visit, as well as percent change or change from baseline compared to placebo. Inferential analysis may be performed if the data permit.

Free serum PCSK9 concentrations will be assessed for all LIB003 patients at Day 1, Week 12, and Week 24. Additional timepoints may be analyzed for patients in support of ADAs.

Immunogenicity Analysis

Immunogenicity data will be listed. ADA data will initially be analyzed for all LIB003 patients on Day 1, Week 12 and Week 24/ET. Additional timepoints will be analyzed for those patients confirmed ADA positive at Week 24/ET.

Pharmacokinetic Analysis

PK will be summarized for all LIB003 patients at Week 12 and Week 24/ET. Additional PK timepoints may also be summarized to support the population PK plan or in support of ADAs.

Safety Analysis

The safety endpoint data will be summarized for the Safety Population, which is defined as all patients who receive at least 1 dose of study drug. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the AEs and serious AEs (SAEs) will be summarized by overall number of AEs, severity, and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of AEs will be summarized by system organ class, preferred term, and treatment group. For AEs and SAEs of special interest, a risk difference along with the 95% confidence interval (CI) will be used to compare the treatment groups.

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

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

Deaths and CVEs will be collected and will be adjudicated by an independent committee. Events that are adjudicated as a “CVE” will be listed and summarized in the current study. In addition, all Phase 3 studies will collect CVEs, and a summarization by treatment group will be performed on the integrated (across all Phase 3 studies) data. Additional details regarding the CV-specific events and their definitions will be included in the CVE adjudication charter.

SAMPLE SIZE DETERMINATION:

The number of patients is based on administration of LIB003 300 mg Q4W (≤ 31 days) achieving at least 95% power to detect a statistically significant difference in LDL-C at both Week 24 and at the mean of Weeks 22 and 24 compared to the placebo group at 2-sided alpha level of 0.05, assuming a common standard deviation of 17.5% for percent change in LDL-C and a treatment difference of 50% as determined by literature review. In terms of safety, while the number of patients is not based on statistical consideration, there is an 80% probability of observing at least 1 occurrence in an LIB003 treatment group of any AE which would occur with a 24% incidence in the population from which the sample is drawn. Approximately 600 patients will participate in this clinical study, including 400 to receive LIB003 and 200 to receive placebo.

SITES: Up to 60 sites in the United States, Canada, Central and South America, Europe, South Africa, Asia, Australasia, and the Middle East

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
BMI	Body mass index
CAD	Coronary artery disease
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CI	Confidence interval
CK	Creatinine kinase
CRA	Clinical research associate
CV	Cardiovascular
CVD	Cardiovascular disease
CVE	Cardiovascular events
DILI	Drug-induced liver injury
DLC	Dutch Lipid Clinics
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EL	Eligibility lipid
Enrollment	The day patient signs the informed consent and first procedure is performed
ESC	European Society of Cardiology
ET	Early Termination
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	Hepatitis B
HbA1c	Glycated hemoglobin

Abbreviation	Definition
HCV	Hepatitis C
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ISR	Injection site reaction
ITT	Intent-to-Treat
IUD	Intrauterine device
IV	Intravenous(ly)
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	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LLN	Lower limit of normal
LOCF	Last post-baseline observation carried forward
Lp(a)	Lipoprotein (a)
mAb	Monoclonal antibody
MI	Myocardial infarction
mITT	Modified Intent-to-Treat
NAb	Neutralizing antibody
OLE	Open-label extension
OM-3	Omega-3 fatty acids
OTC	Over-the-counter
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
Pharmacy Manual	Manual provided by the Sponsor or CRO containing detailed information on study drug (LIB003 or placebo), receipt and storage, preparation (SC), and drug accountability
PK	Pharmacokinetic(s)
PVD	Peripheral vascular disease
Q2W	Every 2 weeks
Q4W (≤ 31 days)	Monthly
RL	Repeat lipid
SAD	Single ascending dose

Abbreviation	Definition
SAE	Serious adverse event
SB	Simon Broome
SC	Subcutaneous(ly)
SE	Standard error
siRNA	Short interfering ribonucleic acid
SOC	Standard of care
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Introduction

Familial hypercholesterolemia (FH) is the most common autosomal dominant disorder in society that if untreated, results in significant morbidity and mortality from premature atherosclerotic cardiovascular (CV) disease (ASCVD). While the clinical condition of FH was described by the Norwegian physician, Muller, 80 years ago in 1938; it was nearly 30 years later in 1964, that it was officially classified as an inherited disorder.^{1,2} It remained until the 1970s before the underlying defect was elucidated by Brown and Goldstein who discovered the low-density lipoprotein (LDL) receptor (LDLR) and that the elevated LDL cholesterol (LDL-C) resulted from reduced, or lack of, clearance of LDL-C from the circulation leading to rapid accumulation of cholesterol in the arterial wall and accelerated atherosclerosis.³ With the advent of genetic analysis, we now know FH is caused predominantly by mutations in the LDLR gene and less commonly from mutations in apolipoprotein (apo) B100 and proprotein convertase subtilisin/kexin type 9 (PCSK9). Very rarely a double mutation affecting LDLR associated protein 1 (LDLRAP1) results in a homozygous FH (HoFH) phenotype, autosomal recessive hypercholesterolemia (ARH).⁴

Prior to the ability to determine specific genetic defects, FH was, and still is in the vast majority of countries and patients, defined and diagnosed by clinical criteria into 2 phenotypes: the more common heterozygous FH (HeFH) with an approximate prevalence of 1 in 250 to 1 in 500 of the general population and the rare HoFH with an estimated prevalence of 1 in 1,000,000.⁴ In some countries, most notably Canada, South Africa, and Lebanon, significantly higher prevalence has been reported in subpopulations due to founder genes that spread in these closed communities many generations ago. Over the last 10 to 15 years based on genetic analysis combined with cascade screening, the prevalence of both HoFH and HeFH has been shown to be significantly higher, ranging from 1 in 125 to 200 for HeFH and 1 in 160,000 to 300,000 for HoFH. However, many of the genetically determined HoFH and HeFH have lower LDL-C levels, the hallmark of the disorder and the main factor driving early atherosclerosis, and often lack the physical characteristics used in the phenotypic classifications.^{4,5} The HeFH phenotype is characterized by LDL-C levels of 200 to 400 mg/dL (2 to 3 times the average levels in non-FH patients), tendon xanthoma, and premature coronary artery disease (CAD). If untreated, the cumulative risk of a coronary event in men by age 30 years is 5%, by age 40 years it is 20%, and by age 60 years it is >60%; while in women, who do not smoke, it is delayed by 10 years.^{6,7} The clinical (phenotype) diagnosis, based on LDL-C, personal and family history and clinical examination, is made most commonly using either the Dutch Lipid Clinics (DLC) criteria which uses a scoring system and classifies HeFH patients into 'definite', 'probable', 'possible', and 'unlikely' for presence of FH and the Simon Broome (SB) classification which using similar lipid and clinical findings classifies potential FH patients in 'definite' or 'possible' categories (see [Appendix C](#) and [Appendix D](#), respectively). The HoFH phenotype manifests with LDL-C levels >500 mg/dL, skin and tendon xanthoma beginning soon after birth, and if untreated, CAD prior to age 20. There is, however, some overlap in the clinical phenotype and LDL-C levels between HeFH and HoFH when assessed by genotype.

Monoclonal antibodies (mAbs), Repatha® (evolocumab) and Praluent® (alirocumab), bind to PCSK9 and prevent it from binding to the LDLR, which result in a rapid recycling of LDLRs, have demonstrated excellent reduction in LDL-C of 60% and 51%, respectively, in HeFH

patients.^{8,9} Inclisiran, a novel short interfering ribonucleic acid (siRNA) which inhibits hepatic PCSK9 production and reduces PCSK9 in the circulation, has demonstrated a 49.5% placebo-adjusted reduction in LDL-C, at a time point 60 days post last dose in a 180 day dosing interval regime, in a recently completed HeFH study.¹⁰ Based on these results, these compounds have been, or may soon be, approved for the treatment of HeFH and have now become part of standard of care (SOC) along with statins and ezetimibe.^{11,12, 13}

Furthermore, recent update to guidelines have defined lower goals for LDL-C achievement, especially in CVD, very- high risk primary prevention and FH patients (Table 1 below).

Table 1. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias¹¹

Recommendations
In secondary prevention for patients at very-high risk an LDL-C reduction of $\geq 50\%$ from baseline [1] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
In primary prevention for individuals at very-high risk but without FH an LDL-C reduction of $\geq 50\%$ from baseline [1] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.
In primary prevention for individuals with FH and at very-high risk an LDL-C reduction of $\geq 50\%$ from baseline [1] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.
In patients at high risk, an LDL-C reduction of $\geq 50\%$ from baseline [1] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.
In individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.
In individuals at low risk, an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.
1. The term “baseline” refers to the LDL-C level in a person not taking any LDL C-lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications. ASCVD = atherosclerotic cardiovascular disease; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol. Source: Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. <i>Eur Heart J.</i> 2020;41(1):111-188

LIB003 is an anti-PCSK9 small binding protein consisting of an Adnectin-fused human serum albumin in order to prevent its rapid renal clearance and enhance its half-life in circulation. As outlined in greater detail below, LIB003 has been shown in Phase 1, 2 and 2b clinical studies to be a highly selective and potent inhibitor of PCSK9 and provide substantial, additional LDL-C lowering when added to stable and maximally tolerated statin, or statin plus ezetimibe, similar to existing mAb treatments.

1.2 Background Information

1.2.1 Nonclinical

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. The human serum albumin contains an alanine substituted for the naturally occurring cysteine at residue 34, which extends the half-life of LIB003 to approximately 12 days. 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 the 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 SC therapy for the reduction of LDL-C in patients with HoFH, HeFH, ASCVD, or a 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.^{14,15,16} To assess the overall toxicity risk of exposing human patients 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 shown in numerous studies with mAbs that inhibit PCSK9, inhibition with LIB003 is not expected to adversely impact the CV system since both PCSK9-null mice and compound heterozygous humans with PCSK9 loss-of-function mutations exhibit no discernable CV phenotype.^{17,18} Moreover, extensive clinical studies inhibiting PCSK9 with mAbs have shown only CV benefit.^{19,20,21} Evaluation of the effect of LIB003 on the CV, 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 CV, 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.

1.2.2 Clinical - Phase 1

The Phase 1, single ascending dose (SAD) study was conducted in 63 subjects, 45 on LIB003 and 18 on placebo, who were monitored post-dose for at least 43 days. This study assessed SC doses of LIB003 25 mg, 75 mg, 150 mg, 300 mg, and 600 mg in healthy subjects on no lipid lowering therapy who had baseline LDL-C ≥ 100 and ≤ 190 mg/dL, and SC doses of LIB003 150 mg and 300 mg in subjects on stable statin therapy who had baseline LDL-C ≥ 100 mg/dL. The 300 mg and 600 mg doses were also evaluated in healthy subjects when dosed IV. All subjects had triglyceride (TG) levels ≤ 250 mg/dL.

1.2.2.1 Safety

Overall, LIB003 was safe and well tolerated following both single SC and IV dosing in healthy subjects and in subjects with hypercholesterolemia on statin therapy at 150 mg and 300 mg administered SC. There were no deaths or discontinuations due to AEs. A total of 6 of 18 (33%) placebo subjects and 13 of 45 (29%) LIB003 subjects reported at least 1 treatment-emergent adverse event (TEAE); none of the TEAEs were considered serious or drug related. The most common AEs reported (by more than 1 subject) were respiratory infections, gastrointestinal, eye (blurred vision), central nervous system (headache), and musculoskeletal disorders; all other AEs were reported by 1 subject only. None appeared to be dose related or

occurred more frequently in LIB003-treated subjects compared to placebo. There were no injection site reactions (ISRs).

One of the AEs that was considered clinically significant occurred in a 39-year-old male subject who received 300 mg LIB003 IV and experienced swelling of his lips 48 hours after study drug. This was confirmed on examination as mild, not affecting speech, food, or fluid intake. The subject denied any other symptoms, such as rash or pruritus. Antihistamines were administered and the swelling subsided after 2 to 3 days without further intervention.

There were no other clinically significant changes or trends in remarkable vital sign measurements or on, physical examination findings, or clinically remarkable trends from baseline to discharge. There were no clinically remarkable trends observed in laboratory findings. There were no AEs based on ECG findings or any findings that were assessed as clinically significant by the Investigator.

Based on a titer of $>4 \times$ minimum required dilution used for assessment of ADAs in prior PCSK9 mAb studies, 3.3% (2/61) patients were considered to have ADAs.¹⁷ Neither of these were considered to be clinically relevant based on a lack of pharmacokinetic (PK) or /pharmacodynamic (PD) effect or safety signals, including ISRs and absence of NABs. ADAs were not detected in any of the placebo patients. Consistent with the lack of PK/PD impact, subsequent testing of ADA positive patients was negative for treatment-induced NABs.

1.2.2.2 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 that were not on lipid-lowering therapy and receiving ≥ 150 mg of LIB003. While the 300 mg dose maintained 99% suppression of free PCSK9 for 29 days, the 150 mg dose showed decreased free PCSK9 of 12% in subjects not on non-lipid lowering therapy and 54% in subjects on statins. The reduced effects in free PCSK9 were reflected in fewer reductions of LDL-C and apo B in statin-treated subjects, with greater reductions maintained in subjects not on lipid lowering therapy. Subsequently, the 150 mg dose did not reduce free PCSK9 or LDL-C sufficiently in all statin-treated subjects 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 Q4W (≤ 31 days) SC: 150 mg, 300 mg, and 350 mg.

1.2.3 Clinical - Phase 2

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 CV disease (CVD), on stable maximal tolerable statin and/or ezetimibe that 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 61 patients in the LIB003 treatment groups (21 on 150 mg, 19 on 300 mg, and 21 on 350 mg) and 20 patients on placebo. 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 mAb, while the second patient withdrew after receiving the first dose due to conflict with her work schedule.

1.2.3.1 Safety

LIB003 was safe and well tolerated following multiple SC dosing. There were no deaths or discontinuations due to AEs. The incidence of TEAEs was similar across placebo and LIB003 dose groups; 10% (2/20) of placebo and 6.6% (4/61) of LIB patients reported TEAEs considered related to study drug. Serious AEs (SAEs) occurred in 1 of 20 (5.0%) of patients in the placebo group (malignant melanoma), 1 of 21 (4.8%) in the LIB003 150 mg group (aortic stenosis), 2 of 19 (10.5%) in the LIB003 300 mg group (abdominal hernia, osteoarthritis), and 2 of 21 (9.5%) in the LIB003 350 mg (seroma, transient ischemic attack [TIA]) group. All SAEs were considered not related to study drug, did not result in discontinuation from the study, and were reported as recovered/resolved by the end of the study.

There were no other clinically significant changes or trends in vital sign measurements or on physical examination findings from baseline to discharge. There were no clinically remarkable trends observed in laboratory findings. There were no AEs based on ECG findings or any findings that were assessed as clinically significant by the Investigator.

Based on a titer of $>4 \times$ minimum required dilution used for assessment of ADAs in prior PCSK9 mAb studies, 3.3% (2/61) patients were considered to have ADAs.¹⁹ Neither of these were considered to be clinically relevant based on a lack of pharmacokinetic (PK) or pharmacodynamic (PD) effect or safety signals, including ISRs and absence of NABs. ADAs were not detected in any of the placebo patients. Consistent with the lack of PK/PD impact, subsequent testing of ADA positive patients was negative for treatment-induced NABs.

1.2.3.2 Efficacy

The coprimary efficacy 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 were achieved ($p < 0.0001$) for all 3 doses (see Analysis of Variance of Low-Density Lipoprotein Cholesterol (Calculated by Friedewald Formula) for the LIB003-002 Study – Intent-to-Treat Population). However, maximal and stable changes were best seen with the 300 mg dose [least-squares mean (standard error [SE]; 95% confidence interval [CI]) 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 2. Analysis of Variance of Low-Density Lipoprotein Cholesterol (Calculated by Friedewald Formula) for the LIB003-002 Study – Intent-to-Treat Population

Visit Statistic	LIB003 150 mg (N=12)	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; vs = versus. Source: LIB003-002 Clinical Study Report			

Based on the results, the dose of 300 mg SC Q4W (≤ 31 days) was selected for the Phase 2b open-label extension (OLE) (LIB003-010) study and the Phase 3 studies, including the current LIB003-004 study.

In the Phase 2b, 52-week OLE study (LIB003-010) with SC LIB003 300 mg Q4W (≤ 31 days), 32 patients from the Phase 2 (LIB003-002) study were enrolled including 10 who had positive ADAs at any titer. Following an approximately 3-month treatment hiatus, all patients were negative for LIB003 ADAs at study initiation. LIB003 was well tolerated and safe in the 52-week OLE study, and in the 88% of patients who were also on LIB003 in the 12-week Phase 2 study total exposure to LIB003 was up to 64 weeks. A total of 26 patients completed the study, with 1 patient withdrawing due to an AE of shoulder pain. There were no deaths and 3 SAEs, none of which were considered related to treatment. LIB003 showed no unexpected or significant adverse clinical or laboratory safety signals. ISRs were infrequent and mild. ADAs were seen in 53% of patients with 2 patients having transitory positive Nabs in-vitro tests without any documented impact on LDL-C, free PCSK9 or association with ISRs. LDL-C reductions were 64% from baseline at time of entry in the OLE and mean free PCSK9 suppression was maintained at trough of $>80\%$.

1.2.4 Clinical - Phase 3

A Phase 3 randomized, open-label, cross-over, global study comparing LIB003 to evolocumab in males and females aged ≥ 10 years with HoFH is currently ongoing in the United States, Norway, Israel, South Africa, Turkey, and India with approximately 50% of the planned 70 patients currently enrolled. All patients already documented to be on a PCSK9 mAb, either evolocumab or alirocumab, are required to have a ‘washout’ of the mAb of ≥ 8 weeks following the last dose, while continuing stable doses of oral therapy (statin with or without ezetimibe or other allowed oral lipid lowering agents) prior to randomization to either evolocumab 420 mg Q4W (≤ 31 days) or LIB003 300 mg Q4W (≤ 31 days) for 24 weeks (Period A). At Week 24, all patients will undergo a second washout of ≥ 8 weeks post last dose of study drug and will then be crossed over to LIB003 if they were on evolocumab and vice versa for the next 24 weeks (Period B).

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

1.3 Rationale

HeFH patients are a group with high risk for CVD and an unmet medical need for further LDL-C reduction, as the majority without clinical CVD do not achieve LDL-C levels of <70 or <100 mg/dL, and those with CVD <40 or <55 mg/dL, as recommended by national or international treatment guidelines (Table 1 above)^{11,12,13}. The PCSK9 mAbs, evolocumab, and alirocumab, have been able to achieve significant further LDL-C reduction when added to statins and ezetimibe drug therapy and are now the SOC for HeFH where these agents are both available and affordable. Alirocumab lowers LDL-C 45% to 60% depending on dose and dose frequency, with the most commonly used 75 mg every 2 weeks (Q2W) being the least effective and 150 mg Q2W the most effective. Both doses are administered as SC injections in 1 mL. A 300 mg (2 mL) dose given Q4W (≤ 31 days) is also available and reduces LDL-C approximately 50%. Evolocumab, is currently the most effective of the PCSK9 inhibitors and reduces LDL-C 60% at both 140 mg Q2W SC in a 1 mL auto-injector or 420 mg Q4W SC, administered either as multiple (3) 1 mL auto-injectors or a slow (9-minute) infusion device (Pushtronix®). Inclisiran, an siRNA, currently awaiting regulatory and marketing approval for FH, is a SC 1.5 mL injection administered by medical personnel at the start of treatment, then again after 90 days and every 180 days thereafter. At the time of the next 180 day dose, LDL-C is reduced 46% to 48% although maximal reductions, which occur 60 days post-dose, reach 55%.^{8-10,22} Based on a need for more effective LDL-C reductions to meet lower goals, less frequent self-administered dosing, and smaller doses combined with good tolerability and safety, LIB003 fills the current gap in potential therapeutic options for PCSK9 inhibition, especially in patients with more severe LDL-C levels such as in FH and also in children and adolescents.

This is a randomized, double-blind, placebo-controlled, Phase 3 study with LIB003 300 mg SC Q4W (≤ 31 days) of 24 weeks duration. This duration was determined to be the most ethical and optimal for a placebo-controlled design for an HeFH population. Approximately 600 males and females aged ≥ 18 years who fulfill the inclusion and exclusion criteria will be enrolled at up to 60 sites in the United States, Canada, Central and South America, Europe, South Africa, Asia, Australasia, and the Middle East. Patients will be randomized in a 2:1 ratio to LIB003 (400 patients) or placebo (200 patients) administered SC Q4W (≤ 31 days). Patients stable on maximal tolerable statin with or without ezetimibe and other allowed oral LDL-C lowering agents with or without an approved PCSK9 mAb (alirocumab or evolocumab) will be eligible. Patients currently or recently on evolocumab or alirocumab will undergo a washout period of ≥ 4 to ≥ 8 weeks (depending on drug and dosing schedule) prior to being randomized on Day 1. The washout period following the last dose of alirocumab or evolocumab will be ≥ 4 weeks for patients on a Q2W dosing schedule at doses of 75 mg, 140 mg, or 150 mg or ≥ 8 weeks for patients on a Q4W dosing schedule at doses of 300 mg or 420 mg. Patients who are documented to have been off these drugs for the required ≥ 4 to ≥ 8 weeks since their last dose at screening may proceed directly to randomization if they meet inclusion/exclusion criteria at screening. For those patients on background PCSK9 mAb therapy the washout period was determined to be as short as possible to achieve stable baseline LDL-C levels prior to randomization. Patients who have been on inclisiran will not be eligible unless they will have been off the drug for ≥ 360 days since the last dose at time of randomization. All patients will then be randomized to either LIB003 300 mg Q4W (≤ 31 days) or

placebo (2:1 respectively) for 24 weeks. The rationale for the LIB003 300 mg SC Q4W (≤ 31 days) dose selection is described in [Section 5.2](#).

Patients completing treatment will be eligible to continue into a 72-week, OLE study under a separate protocol and informed consent (see [Figure 1](#)).

1.4 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 possible reduction in LDL-C.

LIB003 at doses of 300 mg administered SC was shown to reduce LDL-C levels and was safe and well tolerated in both a Phase 2 multiple dose 12-week clinical study and a Phase 2b 52-week OLE study. Thirty-two patients participated in both studies with most obtaining 15 months total exposure to LIB003.

LIB003 has also been well tolerated in nonclinical studies following 26 weeks of weekly dosing at ≤ 100 mg/kg and in clinical studies in over 100 patients at doses up to 600 mg that have been conducted to date, and which have demonstrated an acceptable safety profile for LIB003 to support the initiation of this Phase 3 clinical study. Therefore, the risk to patients in this study is considered low.

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objectives

The coprimary objectives of this study are to assess the LDL-C (calculated by Friedewald formula) reductions at Week 24 and the mean of Weeks 22 and 24 (calculated by Friedewald formula), with Q4W (≤ 31 days) dosing of LIB003 300 mg administered SC compared to placebo, in patients with HeFH on a stable diet and maximally tolerated oral LDL-C lowering drug therapy.

2.1.2 Secondary Objectives

The secondary objectives of this study will be assessed similarly to the coprimary objectives:

- To re-assess the LDL-C lowering effects with LDL-C calculated by Hopkins formula or preparative ultracentrifugation;
- To assess safety and tolerability of LIB003 in HeFH;
- To assess the PD effects of 300 mg LIB003 Q4W (≤ 31 days) on serum unbound (free) PCSK9 concentrations;
- To assess the effects of LIB003 on serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and TG;
- To assess the effects of LIB003 on apo B and lipoprotein (a) (Lp[a]) serum concentrations;
- To assess the PK of LIB003 and total PCSK9 following 300 mg Q4W (≤ 31 days) SC doses of LIB003;
- To assess the frequency and level of ADAs (immunogenicity) following multiple SC doses of LIB003; and
- To assess percentage of patients achieving current ESC/EAS guidelines.

2.1.3 Exploratory Objectives

The exploratory objectives of this study will be assessed similarly to the coprimary objectives:

- To assess the LDL-C response based on underlying genetic variants associated with HeFH;
- To assess the effects on other lipid and CV risk biomarkers as appropriate.

2.2 Endpoints

2.2.1 Primary and Secondary Efficacy Endpoints

The coprimary efficacy endpoints are the percent change from baseline (Day 1) compared to placebo in LDL-C level (by Friedewald formula) at Week 24 and LDL-C level (by Friedewald formula) at mean of Weeks 22 and 24.

The secondary endpoints will be summarized similarly to the primary endpoints (absolute and/or percent change from baseline compared to placebo):

- Percent change in:
 - LDL-C level at Week 24 (by Hopkins formula);
 - LDL-C level at Week 24 (by preparative ultracentrifugation); and
 - LDL-C level at mean of Weeks 22 and 24 (by Hopkins formula);
- Absolute and percent change (where not assessed prior) from baseline (Day 1) in LDL-C level by Friedewald and Hopkins formulas at all visits (Weeks 4, 8, 12, 16, 20, 22, and 24);
- Serum unbound (free) PCSK9 concentrations in LIB003 patients at Day 1, Week 12 and Week 24. Other visits including Weeks 4, 8, 12, 16, and 20 will be measured in response to ADAs in LIB003 patients. Samples from placebo patients will be stored;
- Absolute and percent change from baseline (Day 1) in TC, HDL-C, non-HDL-C, VLDL-C, and TG at all visits (Weeks 4, 8, 12, 16, 20, 22, and 24);
- Absolute and percent change from baseline (Day 1) in apo B and Lp(a) serum concentrations to Week 24; and
- Percentage of patients achieving current ESC/EAS guidelines.

2.2.2 Immunogenicity Endpoints

ADAs will be measured at Day 1, Week 12 and Week 24/Early Termination (ET) in LIB003 patients. Other visits including Weeks 4, 8, 16, and 20 may be measured if ADAs are detected at Week 24/ET in LIB003 patients. Samples from placebo patients will be stored for potential future assessment.

2.2.3 Exploratory Endpoints

- The percent change from baseline (Day 1) in LDL-C level to Week 24 by HeFH variant; and
- The percent change from baseline (Day 1) in other lipid and CV risk biomarkers to Week 24.

2.2.4 Pharmacokinetic Endpoints

The PK concentration for LIB003 and total serum PCSK9 will be measured at Week 12 and Week 24/ET in LIB003 patients. Total serum PCSK9 will also be measured at Day 1. Other visits including Weeks 4, 8, 16, and 20 may be measured to support the population pharmacokinetic plan or the presence of ADAs in LIB003 patients. Samples from placebo patients will be stored for potential future assessment.

2.2.5 Safety Endpoints

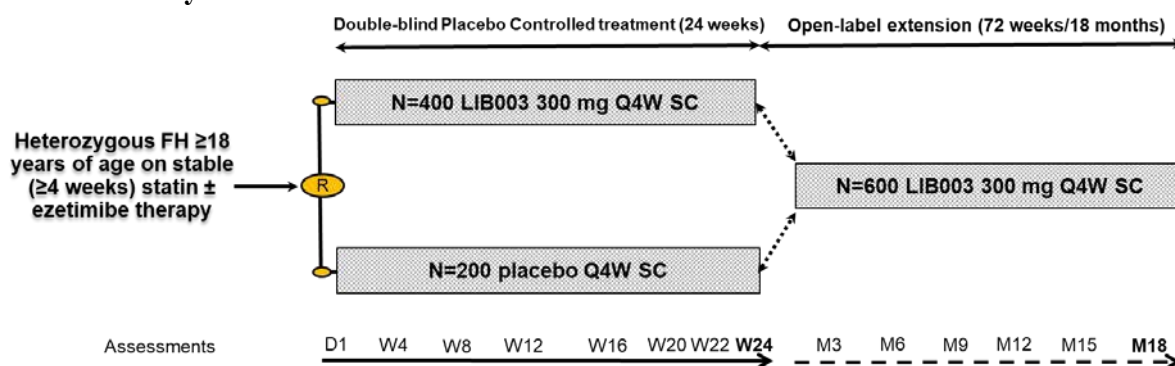
Safety endpoints are AEs, including CVEs and all-cause mortality; safety laboratory parameters (chemistry, hematology, coagulation, and urinalysis), with particular attention to hepatic (eg, alanine transaminase [ALT]/aspartate transaminase [AST], total bilirubin, alkaline phosphatase) and skeletal muscle (ie, creatine kinase [CK]) toxicities; 12-lead ECGs; ISRs; physical examinations; and vital signs.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled, Phase 3 study with LIB003 300 mg SC Q4W (≤ 31 days) of 24 weeks duration. Approximately 600 males and females aged ≥ 18 years who fulfill the inclusion and exclusion criteria will be enrolled at up to 60 sites in the United States, Canada, Central and South America, Europe, South Africa, Asia, Australasia, and the Middle East. Patients will be randomized in a 2:1 ratio to LIB003 (400 patients) or placebo (200 patients) administered SC Q4W (≤ 31 days). The study will consist of a Screening Period and a Treatment Period. The total study duration will be up to 35 weeks which includes up to an 11-week Screening Period (which may include up to an 8-week washout) and 24 weeks of study drug treatment (Figure 1).

Figure 1. LIB003-004 Phase 3 Study Design: Heterozygous Familial Hypercholesterolemia Study



D = day; FH = familial hypercholesterolemia; M = month; Q4W (≤ 31 days) = monthly; SC = subcutaneously; W = week.

Screening Period: Depending on if patients are “Randomization Ready” or require “Washout and Diet/Lipid Stabilization” they will undergo variable Screening Periods as follows (see Figure 2). The Screening Period may be extended, or a patient may be rescreened once upon review and approval.

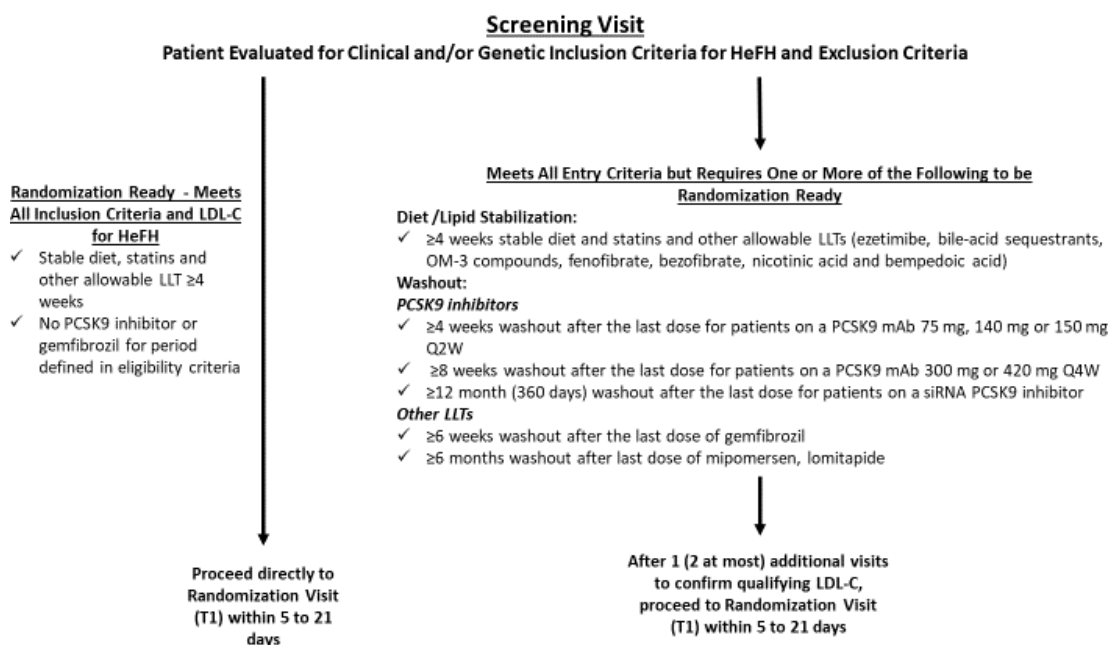
1. “Randomization Ready”: Patients who are following an appropriate diet and are stable for ≥ 4 weeks on statins and other allowed oral lipid lowering therapy and have not received a PCSK9 inhibitor for the period defined in the exclusion criteria will proceed directly to the Randomization Visit (Day 1) if they meet all other eligibility criteria. Patients whose LDL-C is up to 5 mg/dL below the defined entry level based on very-high risk for CVD or high risk for CVD or triglycerides >400 to 450 mg/dL may have 1 fasting lipid repeat profile (Screening Visit repeat lipid [RL]). After meeting all entry criteria, the Randomization Visit should occur no earlier than 5 days and no later than 21 days from the Screening Period.

2. “Washout and Diet/Lipid Stabilization”: Patients who meet clinical and or genetic entry criteria (other than LDL-C criteria) and requiring washout of lipid lowering agents excluded in the study (see inclusion/exclusion criteria in Sections 4.1 and 4.2) and/or diet and allowed oral lipid lowering drug stabilization (eg, statins, ezetimibe, bile acid sequestrants, omega-3 fatty acids [OM-3], bezafibrate, fenofibrate, nicotinic acid and bempedoic acid) will complete the required washout/stabilization period before having a fasting lipid profile to determine final eligibility (eligibility lipid [EL]). For patients on a PCSK9 mAb at a dose of 75 mg, 140 mg or 150 mg Q2W,

the washout period is ≥ 4 weeks after the last dose; for those on 300 mg or 420 mg Q4W, the washout period is ≥ 8 weeks following last dose (see inclusion/exclusion criteria in [Sections 4.1](#) and [4.2](#)). For patients who have received an siRNA PCSK9 inhibitor the washout period is ≥ 360 days post last dose.

Patients, who after the required washout/stabilization at the EL Visit have an LDL-C up to 5 mg/dL below the defined entry level based on CVD or no CVD or TG >400 to 450 mg/dL may have 1 fasting RL profile. After meeting all entry criteria, the Randomization Visit should occur no earlier than 5 days and no later than 21 days from washout/stabilization.

Figure 2. LIB003-004 Phase 3 Screening Tree



HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT = lipid lowering therapy; mAb = monoclonal antibody; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = every 2 weeks; Q4W (≤ 31 days) = monthly; siRNA = short interfering ribonucleic acid.

Double-Blind Treatment Period: After confirmation of qualifying fasting Friedewald LDL-C and TG values and all other inclusion and exclusion criteria, eligible patients will be randomized to either LIB003 or placebo (2:1 respectively) and enter the 24-week, double-blind Treatment Period. Randomization will be via an interactive response technology (IRT) on Day 1. Both LIB003 300 mg (400 patients) or placebo (200 patients) will be administered SC Q4W (≤ 31 days). Patients will be stratified based on very-high risk for CVD or high risk for CVD to ensure balance across treatment groups. Patients will be reminded at all visits as to the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

Following randomization and dosing on Day 1, patients will be seen in the clinic Q4W (≤ 31 days) for 20 weeks and then at 2-week intervals for Weeks 22 and 24. All patients will receive doses of LIB003 300 mg Q4W (≤ 31 days) or placebo on Day 1 and Weeks 4, 8, 12, 16, and 20. In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified

visits during the study. An aliquot of the lipid specimen at Day 1 and Week 24/ET will be stored for later analysis of exploratory lipid and CV risk biomarkers. A deoxyribonucleic acid (DNA) sample will be obtained at Day 1 and will be analyzed, if necessary, for genetic confirmation and assessment of variants known to cause HeFH. All lipid, PK, and PCSK9 results following the baseline measurements on Day 1 will be blinded to the Investigator and all site and Sponsor personnel involved in the study. Final safety assessments will include AEs and the results from physical examinations, ECGs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. ISRs will be assessed at each visit drug is administered. Blinded safety, ISR, and lipid data will be reviewed by a Data Safety Monitoring Board (DSMB) at pre-determined intervals throughout the program. If indicated by these assessments, ADAs will be analyzed during study conduct to support safety monitoring. Patients with confirmed positive ADAs titers will have NAbs, PK (LIB003) and free PCSK9 assessed and may be further characterized for isotype, binding site, and affinity.

Patients completing the base study (LIB003-004) will be eligible to enter an OLE study, under a separate protocol and informed consent, where they will receive LIB003 300 mg Q4W (≤ 31 days) for an additional 72 weeks.

Patients on LIB003 who test positive for binding, non-NAbs and have clinical sequelae that are considered safety-related at the final visit of this study (Week 24/ET) may be asked to return for additional Q4W (≤ 31 days) follow-up testing if they terminate the base study (LIB003-004) and do not enter the OLE study.

Patients on LIB003 who test positive for NAbs at the final visit of this study (Week 24/ET), who do not enter the OLE study and who have no clinical sequelae, will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable, considered stable or the patient has been followed for a period of at least 12 months. For patients who test positive, but have not received active drug, follow-up testing will not be required.

3.2 Stopping Rules

Patient Dose-Limiting Toxicity:

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

- Unexplained ALT and/or AST $> 5 \times$ upper limit of normal (ULN) (confirmed on 2 consecutive occasions at least 4 days apart);
- ALT and/or AST $> 3 \times$ ULN AND total bilirubin $> 2.0 \times$ ULN for patients without Gilbert's syndrome and $2 \times$ baseline for those with Gilbert's syndrome (confirmed by immediate repeat); or
- ALT or AST $> 3 \times$ ULN (confirmed by immediate repeat) with the appearance or worsening of symptoms considered 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.

Study Termination:

The study will be terminated if either of the following events occur:

- ≥ 2 patients administered LIB003 300 mg with the same drug-related SAE as determined by the Sponsor and DSMB; or
- ≥ 2 patients administered LIB003 300 mg with ALT and/or AST $> 5 \times$ ULN (confirmed on 2 consecutive occasions at least 4 days apart and with no alternative likely etiology).

The Sponsor reserves the right to terminate the study or the participation of a study site at any time. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue testing the study drug; and/or
- Failure of the Investigator to comply with Good Clinical Practice (GCP).

3.3 Study Indication

LDL-C reduction in patients with ASCVD, high risk of ASCVD, HoFH, or HeFH without CVD who require additional LDL-C reduction.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Provision of written and signed informed consent prior to any study-specific procedure;
2. Male or female, 18 years of age at the first Screening Visit;
3. Weight of 240 kg (88 lbs) and body mass index (BMI) 27 and $\geq 42 \text{ kg/m}^2$;
4. Diagnosis of definite, probable or possible HeFH based either on clinical criteria (Simon Broome register criteria [Appendix C] or Dutch Lipid Clinic [DLC] Network Criteria [Appendix D]) or genotyping and at the defined eligibility visit (screening or post washout/stabilization) a calculated LDL-C (Friedewald) 270 mg/dL (if very-high risk for CVD) or 210 mg/dL (if high risk for CVD) as defined in Appendix E and TG $\geq 400 \text{ mg/dL}$ while on stable lipid lowering oral drug therapy (eg, maximally tolerated statin with or without ezetimibe);

Note: ASCVD encompasses acute coronary syndrome, history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease, including aortic aneurysm, all of atherosclerotic origin.

5. Patients with documentation of inability to tolerate any statin at any dose, or history of rhabdomyolysis, and unable to tolerate any other allowed oral lipid lowering agent, and thus on no lipid lowering therapy must have an LDL-C $\geq 190 \text{ mg/dL}$ (4.9 mmol/L) at the Screening Visit unless they have a documented pathogenic FH variant;

Note: Patients unable to tolerate approved doses of a statin may take lower than approved doses and less frequently than daily as long as the dose and dosing frequency is consistent. Patients with documented intolerance to statins may also participate.

6. On a stable diet²³ and lipid-lowering oral therapies (statins, ezetimibe, bile-acid sequestrants, OM-3 compounds, fenofibrate, bezafibrate, nicotinic acid and bempedoic acid) or combinations thereof for at least 4 weeks (excluded oral lipid lowering agents are defined below in Section 4.2 and include mipomersen, lomitapide, and gemfibrozil);
7. Patients on a PCSK9 mAb at a dose of 75 mg, 140 mg, or 150 mg Q2W must undergo a washout period of 24 weeks after the last dose; for those on a dose of 300 mg or 420 mg Q4W (531 days) the washout period is 28 weeks following last dose. For patients who have received an siRNA PCSK9 inhibitor the washout period is 2360 days post last dose;
8. Females of childbearing potential must be using a highly effective form of contraception if sexually active and have negative urine pregnancy test at the last Screening Visit;

Note: Highly effective methods of birth control include refraining from heterosexual sexual intercourse during the entire period of risk, 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. Menopause is defined as 12 months of spontaneous and continuous amenorrhea in a female 55 years old or 12 months of spontaneous and continuous amenorrhea with a

follicle-stimulating hormone (FSH) level >40 IU/L (or according to the definition of “postmenopausal range” for the laboratory involved) in a female <55 years old unless the patient has undergone bilateral oophorectomy.

9. Male patients will either be surgically sterile or agree to use the following forms of contraception: male or female condom with spermicide and a female partner who is sterile or who agrees to use the following contraceptives; diaphragm or cervical cap with spermicide; or intrauterine device, oral, implantable, or injectable contraceptives; and
10. Male patients must refrain from sperm donation until 90 days following the last dose of study drug.

4.2 Exclusion Criteria

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

1. Use of prohibited oral lipid lowering agents mipomersen or lomitapide within 6 months of screening, gemfibrozil within 6 weeks of the Screening Visit;
2. Low-density lipoprotein or plasma apheresis within 2 months prior to Day 1;
3. Documented history of homozygous familial hypercholesterolemia defined as clinical and/or genetic with true HoFH (ie, identical pathogenic variants), compound heterozygous (ie, 2 different pathogenic LDLR variants) or combined heterozygous (2 different pathogenic FH variants such as LDLR plus Apo B, LDLR plus PCSK9 GOF);
4. History of any prior or active clinical condition or acute and/or unstable systemic disease compromising patient inclusion, at the discretion of the Investigator, including but not limited to clinically significant pulmonary, 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;
5. Females of childbearing potential who are sexually active, not using or unwilling to use a highly effective form of contraception, pregnant or breastfeeding, or who have a positive urine pregnancy test at the last Screening Visit;

Note: Highly effective methods of birth control include refraining from heterosexual sexual intercourse during the entire period of risk, birth control pills or patches, 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.

6. Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate <30 mL/min/ 1.73m^2 at the Screening Visit;
7. Active liver disease or hepatic dysfunction (eg, cirrhosis, alcoholic liver disease, known hepatitis B [HBV] or hepatitis C [HCV], autoimmune hepatitis, liver failure, liver cancer), history of liver transplant, and/or AST or ALT $>2.5 \times$ the ULN as determined by central laboratory analysis at screening (tests that result in ALT or AST up to $3 \times$ ULN may have 1 repeat test to confirm eligibility during the Screening Period);
8. Uncontrolled thyroid disease: hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone (TSH) below the lower limit of normal (LLN) or $>1.5 \times$ ULN,

respectively, at the Screening Visit. If TSH is above/below these cut-off points, the subject can enter if the free T3 is within the reference range. If controlled, then treatment should be stable for at least 3 months prior to the Screening Visit;

9. Uncontrolled Type 1 or Type 2 diabetes mellitus (defined as fasting glucose ≥ 200 mg/dL or glycated hemoglobin (HbA1c) of $\geq 9\%$);
10. Uncontrolled serious cardiac arrhythmia (sustained ventricular tachycardia, frequent non-sustained ventricular tachycardia, any ventricular fibrillation episode, wide-complex tachycardia, atrial fibrillation with rapid ventricular response, and severe second degree or third degree atrioventricular block), MI, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, placement of implantable cardioverter defibrillator or biventricular pacemaker, aortic valve surgery, or stroke within 3 months prior to enrollment (the day patient signs the informed consent and first procedure is performed);
11. Planned cardiac surgery or revascularization;
12. New York Heart Association III-IV heart failure; or patients with last documented left ventricular ejection fraction $< 30\%$ by SOC assessments, eg, echocardiography, cardiac magnetic resonance imaging, nuclear imaging, computed tomography angiography, angiography with ventriculogram, within 12 months;
13. Uncontrolled hypertension defined as evidenced by a reproducible (repeated 5 minutes apart) sitting blood pressure ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic;
14. 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(ies), or receiving other investigational agent(s); such as PCSK9 or Lp(a) siRNA or locked nucleic acid-reducing agents within 12 months of the Screening Visit;
15. Unexplained creatine kinase $> 5 \times$ ULN, unless related to exercise or unusual activity in which case 1 repeat test is allowed;
16. Patients who cannot be available for protocol-required study visits or procedures, to the best of the patient's and Investigator's knowledge;
17. A history, within 6 months prior to screening, of prescription drug abuse, illicit drug use, or alcohol abuse according to medical history;
18. Donated or lost a significant volume (> 500 mL) of blood or plasma within 30 days prior to Day 1;
19. Had a blood transfusion within 4 weeks of randomization or known diagnosis of human immunodeficiency virus;
20. Previous treatment with LIB003 or any adnectin product;
21. Have any other finding which, in the opinion of the Investigator, would compromise the patient's safety or participation in the study; or
22. An employee or family member of the Investigator or study site personnel.

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 for any reason;
- The patient starts on a prescription PCSK9 inhibitor or an excluded lipid lowering agent (see 4.2) unless the latter is stopped immediately, and patient agrees not to continue or restart;
- 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 AE, 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; or
- Termination of the study by the Sponsor or the regulatory authority.

If a patient withdraws from treatment, every effort should be made to ensure the patient continues to complete study visits for the collection of safety information. Withdrawn patients may not be replaced.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the final study visit evaluations (including the collection of endpoint data) at the ET Visit which includes the same evaluations performed at Day 169/Week 24. Study staff including the site Investigators will be trained on the importance of preventing missing data. The reason for patient withdrawal must be documented in the electronic Case Report Form (eCRF). The Investigator should make every effort to obtain information about possible underlying AEs, or other reasons and report the observation as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal. Any AE, CV event, or SAE information elicited must be documented in the patients' source documents and eCRF. If a patient is withdrawn due to an AE, the Investigator will follow the patient until the AE has resolved or stabilized.

At the time of discontinuing from the study, the Study Manager and IRT should be contacted. In accordance with the Declaration of Helsinki and other applicable regulations, a patient has the right to withdraw consent for participation in the study at any time, and for any reason without prejudice to his or her future medical care by the physician or at the institution. The Investigator will clearly document the reason for the consent withdrawal in the medical record and will complete the associated eCRF. **Patients should be followed in the study for protocol specified evaluations of clinical and safety events unless there is written documentation by the Investigator of the patient's withdrawal of consent to all of the following methods of follow-up:**

- Participation in the study follow-up procedures per protocol, either in clinic or by telephone;
- Contact by study personnel even if only by telephone;

- Permission for study personnel to contact an alternative person (eg, family, spouse, partner, legal representative, or physician) even if only by telephone; or
- Permission for study personnel to access and review their medical information from alternative resources (eg, doctor's notes, hospital records).

5 STUDY TREATMENTS

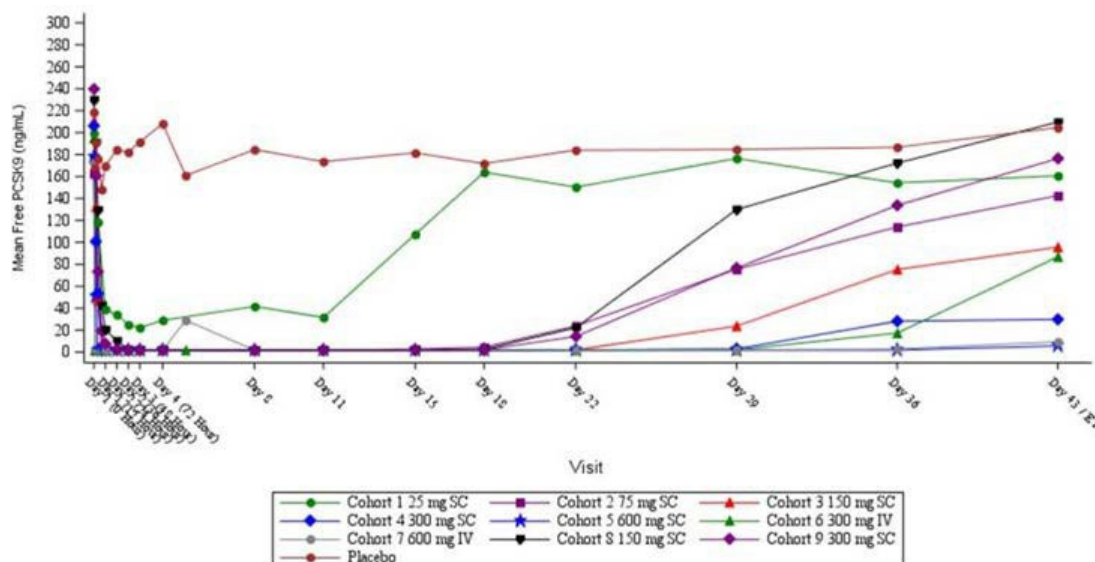
5.1 Treatment Groups

Following determination of eligibility, approximately 600 patients will participate in this Phase 3, efficacy, safety, and tolerance study. Patients will be randomized in a 2:1 ratio to LIB003 (400 patients) or placebo (200 patients) administered SC Q4W (≤ 31 days) over a 24-week Treatment Period.

5.2 Rationale for Dosing

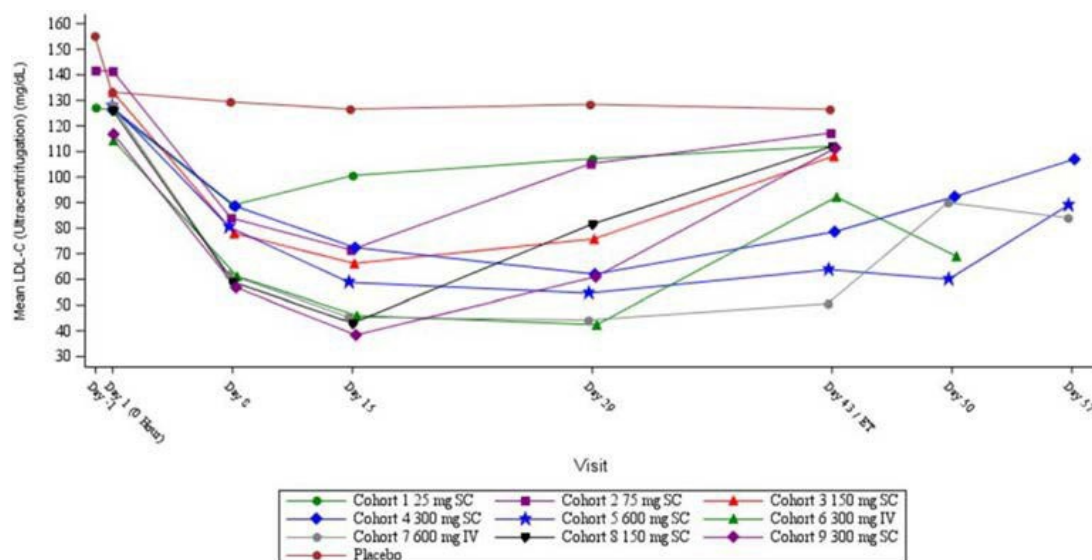
LIB Therapeutics is developing LIB003 with the goal of achieving maximal and stable LDL-C lowering with a 4-week dosing interval. The design and safety results of the LIB003-001 Phase 1 SAD study are described in [Section 1](#). In support of dose selection, Figure 3 and [Figure 4](#) display the Phase 1 study results of free PCSK9 and LDL-C by preparative ultracentrifugation, respectively. Mean reductions in free PCSK9 were rapid with all doses and reached more than 99% within 12 hours and were sustained for 3 to 4 weeks (Days 22 to 29) in the cohorts receiving ≥ 150 mg of LIB003. The 300 mg dose appeared most optimal for Q4W (≤ 31 days) dosing in that it maintained almost maximal suppression of free PCSK9 for 29 days. The reductions in free PCSK9 with the LIB003 dose of 300 mg were reflected in reductions of LDL-C, where greater reductions were maintained for up to 28 days even in patients on statins.

Figure 3. LIB003-001 SAD: Changes in Free PCSK9 With LIB003 by Treatment



ET = Early Termination; IV = intravenous; PCSK9 = proprotein convertase subtilisin/kexin type 9; SAD = single ascending dose; SC = subcutaneous.

Figure 4. Changes in Ultracentrifugation LDL-C by Treatment



ET = Early Termination; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; SC = subcutaneous.

These results were confirmed in the larger Phase 2 study (LIB003-002); the design, safety and overall efficacy of this study are described in [Section 1](#). Patients were randomized to Q4W (≤ 31 days) SC treatment with LIB003 150, 300, or 350 mg or placebo with approximately 20 patients per group. The coprimary efficacy endpoints were LDL-C at Week 12 and mean LDL-C at Weeks 10 and 12. Patients were monitored for an additional 4 weeks through Week 16 for safety. This study included patients on moderate and high intensity statins and some patients with HeFH; groups that are known to have higher baseline PCSK9 levels and increased synthesis of PCSK9.

The coprimary efficacy 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 were achieved ($p < 0.0001$) for all 3 doses; however, maximal and stable changes were best seen with the 300 mg dose: where the LS mean (SE; 95% CI) was -77.3% (6.63%; -90.5%, -64.1%) at Week 12 LOCF and -76.1% (4.99%; -86.0%, -66.2%) at mean of Weeks 10 and 12.

Similar LDL-C and free PCSK9 reductions were maintained for 52 weeks in the OLE study (LIB003-010). In summary to date, no specific risks have been identified in the non-clinical or clinical development of LIB003.

The 300 mg dose selected for Q4W (≤ 31 days) dosing in Phase 3 patients is anticipated to be safe based on the lack of AE findings in clinical studies of human LIB003 exposure up to 600 mg both SC and IV in Phase 1, multiple doses of 300 mg and/or 350 mg SC in Phase 2 including a Phase 2b 52 week open label extension trial, and in the 12-week and 26-week non-human primate GLP toxicology studies, which included both juvenile and sexually mature animals, where steady-state exposure levels were achieved.

5.3 Randomization and Blinding

Patients who have completed the Screening Visit and meet all the inclusion criteria and none of the exclusion criteria will be randomized into the study on Day 1. Patients will be randomized 2:1 to LIB003 300 mg (400 patients) or placebo (200 patients) administered SC Q4W (≤ 31 days). Randomization will be stratified by very-high risk CVD or high-risk CVD. Randomized treatment assignment and randomization numbers will be assigned via IRT and study drug will be dispensed in a double-blind manner. The Sponsor and all key clinical site personnel (Investigator, Sub-Investigator (s), coordinator, etc.) will be blinded to the treatment group for each patient. Patients also will be blinded to the treatment they receive. Because the color of the study drug product and placebo will not be identical, all therapy will be prepared by an unblinded pharmacist and administered by unblinded nurses who will be instructed not to discuss randomized treatment assignments. Neither the pharmacist nor nurse(s) administering the study drug will be involved in any other aspects of the study or patient contact.

All lipid, PSCK9 and PK measurements after Day 1 will be blinded to the Investigator and study personnel involved in the study at both the clinical site and LIB Therapeutics.

5.4 Breaking the Blind

Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of patient safety. The Investigator should contact the Medical Monitor who will allow for the blind to be broken in a qualifying event. When the blind is broken, the reason must be fully documented.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The LIB003 drug product is a 250 mg/mL solution packaged in 1.2 mL volumes (to provide for 1.2 mL extractable volume) in a 2 mL clear glass vial with a stopper and aluminum crimp seal for a single SC injection of 300 mg.

The LIB003 formulation contains 20 mM histidine, 150 mM sodium chloride, 0.02% (w/v) 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

See the Pharmacy Manual for detailed instructions for LIB003 and placebo preparation.

All doses of LIB003 or placebo will be prepared by unblinded pharmacists. 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 and 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.

5.5.3 Study Drug Administration

Study drug (LIB003 or placebo) will be administered by SC injection in either the abdomen, thigh or upper arm (which may be rotated) on Day 1 and Weeks 4, 8, 12, 16, and 20. Study drug will be

administered by unblinded clinic personnel who will not participate further in the evaluation of patients (as described in [Section 5.3](#)).

5.5.4 Treatment Adherence

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

5.5.5 Storage and Accountability

Study drug, LIB003 and placebo, as outlined in the separate Pharmacy Manual, 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 the 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 study nurse in a secure location. Drug accountability records will be available for verification by LIB Therapeutics personnel.

Storage and accountability information will be outlined in a 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:

- Hormone replacement therapy use is only permitted if initiated at least 2 months prior to the Randomization Visit and is anticipated to remain stable throughout the study;
- Medications used to treat AEs 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 (eg, steroids for asthma, bee sting, allergic rash). All therapy and/or medication administered to manage AEs should be recorded in the appropriate eCRF; and
- Any other investigational drug taken within 30 days or 5 half-lives (whichever is longer) prior to screening is excluded.

5.6.2 Restricted Medications and/or Procedures

Restricted medications include, but are not limited to the use of, or treatment with, any prescription lipid-altering drugs other than statins, ezetimibe, bile acid sequestrants, nicotinic acid, bezafibrate, fenofibrate, OMG-3 compounds and bempedoic acid as specified in [Section 4.1](#).

5.6.3 Restrictions and Dietary Guidelines

Patients should be encouraged to continue on an appropriate and stable diet²³ and not participate in strenuous physical activity or exercise from 72 hours prior to all study visits to prevent concomitant increases in CK 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, ezetimibe, and/or other lipid lowering medications and the doses 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 ailment 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. Legally acceptable representatives providing assent for a patient must provide assent in a manner approved by the IRB/IEC and local regulations. A separate informed consent may be required for genetic testing. 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, scientific importance of collecting all data and preventing missing data and other critical issues regarding the clinical study in which they volunteer to participate.

6.2 Study Schedule

A ± 3 -day window is allowed for all clinic visits; unanticipated or unavoidable cancellations due to weather or public holidays may be scheduled within a 5-day window and will not be considered protocol deviations if appropriately documented ([Appendix A](#)). It is important that study medication is dosed within 31 days from the prior dose and earlier than 28 days is preferable rather than >31 days if patients cannot make return visit within 31 days.

It is also important to schedule the next visit *within the 31-day window from the last visit*, and not based on the randomization date. For example, if 3 post randomization visits have occurred at days 27, 26 and 27 then the next visit should be within 28 (± 3) days *post the last visit* and not 28 (± 3) days based on date of randomization which would be potentially outside 31 days from last visit.

All blood and urinalysis samples should be collected while the patient is in a fasted state (≥ 10 hours; ad libitum water is permitted and encouraged), prior to administration of study drug (LIB003 or placebo), and, where feasible, prior to completing other visit assessments, with the exception of body weight.

6.2.1 Screening Visit (Day -77 to Day -5)

Screening procedures must be performed no earlier than 5 days and no later than 77 days prior to commencing randomization and dosing on Day 1. During the PCSK9 washout and diet/lipid stabilization, patients may have up to 2 additional screening visits (Screening Visits EL and RL) for assessment of inclusion/exclusion criteria, including but not limited to lipid profile.

The following procedures will be performed:

- Obtain informed consent, including for DNA/genotyping;
- **Review if patient meets diagnostic criteria for HeFH – if not met, terminate visit;**
- **Evaluate inclusion/exclusion criteria - if not met, terminate visit;**
- Obtain demographics and medical history;
- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks; record prior treatment with evolocumab or alirocumab including dose, dosing frequency, and last dose;

- Obtain height and body weight and calculate BMI;
- Urine pregnancy test (only females of childbearing potential); serum FSH will be measured for women uncertain of post-menopausal status (<1 year since last menses);
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
 - Full safety chemistry panel and hematology;
 - Brief lipid panel; and
 - TSH;
- Perform physical examination;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- For “Randomization Ready” patients, who are documented to have met the criteria for HeFH and have been stable on allowed oral lipid lowering medication and diet for ≥ 4 weeks and not received any PCSK9 mAb for the required period specified in [Section 4.1](#) may proceed directly to randomization (Day 1) if they meet LDL-C entry criteria. Patients whose LDL-C is up to 5 mg/dL below defined entry level based on very-high risk CVD or high-risk CVD or triglycerides >400 to 450 mg/dL may have 1 fasting lipid repeat profile (Screening Visit RL). After meeting all entry criteria, the Randomization Visit should occur no earlier than 5 days and no later than 21 days from the Screening Period;
- For “Washout and Diet/Lipid Stabilization” patients, who meet clinical and/or genetic entry criteria (other than perhaps LDL-C criteria) and are requiring washout of lipid lowering agents excluded in the study (see inclusion/exclusion criteria in [Sections 4](#)) and/or diet and allowed oral lipid lowering drug stabilization (eg, statins, ezetimibe, bile acid sequestrants, OM-3 compounds, bezafibrate, fenofibrate, nicotinic acid and bempedoic acid) will complete the required washout/stabilization period before having a fasting lipid profile to determine final eligibility (EL). For patients on a PCSK9 mAb at a dose of 75 mg, 140 mg or 150 mg Q2W the washout period is 4 weeks after the last dose, for those on 300 mg or 420 mg Q4W (≤ 31 days) the washout period is 8 weeks following last dose (see inclusion/exclusion criteria in [Sections 4.1](#) and [4.2](#)). For patients who have received a siRNA PCSK9 inhibitor the washout period is ≥ 360 days post last dose. Patients, who after the required washout/stabilization at the lipid eligibility visit have an LDL-C up to 5 mg/dL below defined entry level based on very-high risk CVD or high risk CVD or TG > 400 mg/dL to 450 mg/dL may have 1 repeat fasting lipid profile (RL). Following meeting all entry criteria, the Randomization Visit should occur no earlier than 5 days and no later than 21 days from the Screening Period; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.2 Day 1 (Week 0)

The following procedures will be performed:

- Review inclusion and exclusion criteria;
- Update medical history;
- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks; verify the last dose of a PCSK9 mAb and last screening of LDL-C was as specified in the inclusion/exclusion criteria in [Section 4.1](#);
- Randomize patient to double-blind study drug (LIB003 or placebo);
- Obtain body weight;
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
 - DNA/genotyping;
 - Full safety chemistry panel and hematology (and HbA1c);
 - PK;
 - PCSK9 (free);
 - Expanded lipid panel;
 - Immunogenicity; and
 - Exploratory biomarkers (blood samples for exploratory biomarkers will be collected and frozen for potential assessment of additional lipid or CV risk biomarkers);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Perform 12-lead ECG;
- Administer SC doses of blinded study drug (LIB003 or placebo);
- Assess injection site (pre-dose and 15 minutes post-dose);
- Assess AEs;
- Remind patient the importance of returning to the clinic in 28 days (≤ 31 days) for the next dose of study drug; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.3 Day 29 (Week 4)

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks;
- Collect fasting blood samples for the following:

- Brief safety chemistry panel;
- PK;
- PCSK9 (free);
- Brief lipid panel; and
- Immunogenicity;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Administer SC doses of blinded study drug (LIB003 or placebo);
- Assess injection site (pre-dose and 15 minutes post-dose);
- Assess AEs;
- Remind patient the importance of returning to the clinic in 28 days (≤ 31 days) for the next dose of study drug; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.4 Day 57 (Week 8)

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks;
- Collect fasting blood samples for the following:
 - Full safety chemistry panel;
 - PK;
 - PCSK9 (free);
 - Brief lipid panel; and
 - Immunogenicity;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Administer SC doses of blinded study drug (LIB003 or placebo);
- Assess injection site (pre-dose and 15 minutes post-dose);
- Assess AEs;
- Remind patient the importance of returning to the clinic in 28 days (≤ 31 days) for next dose of study drug; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.5 Day 85 (Week 12)

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks;
- Collect fasting blood samples for the following:
 - Brief safety chemistry panel;
 - PK;
 - PCSK9 (free);
 - Brief lipid panel; and
 - Immunogenicity;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Administer SC doses of blinded study drug (LIB003 or placebo);
- Assess injection site (pre-dose and 15 minutes post-dose);
- Assess AEs;
- Remind patient the importance of returning to the clinic in 28 days (≤ 31 days) for the next dose of study drug; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.6 Day 113 (Week 16)

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks;
- Obtain body weight;
- Collect fasting blood samples for the following:
 - Brief safety chemistry panel;
 - PK;
 - PCSK9 (free);
 - Brief lipid panel; and
 - Immunogenicity;
- Perform physical examination;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Administer SC doses of blinded study drug (LIB003 or placebo);
- Assess injection site (pre-dose and 15 minutes post-dose);

- Assess AEs;
- Remind patient the importance of returning to the clinic in 28 days (≤ 31 days) for the next dose of study drug; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.7 Day 141 (Week 20)

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks;
- Collect fasting blood samples for the following:
 - Brief safety chemistry panel;
 - PK;
 - PCSK9 (free);
 - Brief lipid panel; and
 - Immunogenicity;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Administer SC doses of blinded study drug (LIB003 or placebo);
- Assess injection site (pre-dose and 15 minutes post-dose);
- Assess AEs;
- Remind patient the importance of returning to the clinic in 14 days for the Week 22 visit; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.8 Day 155 (Week 22)

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 2 weeks;
- Collect fasting blood samples for the following:
 - Brief lipid panel;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Assess AEs;
- Remind patient the importance of returning to the clinic in 14 days for the Week 24 visit (28 days [≤ 31 days] from the Week 20 visit; and

- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.9 Day 169 (Week 24)/Early Termination

The following procedures will be performed:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 2 weeks;
- Obtain body weight;
- Collect urine sample for urinalysis;
- Urine pregnancy test (only females of childbearing potential);
- Collect fasting blood samples for the following:
 - Full safety chemistry panel and hematology (and HbA1c);
 - PK;
 - PCSK9 (free);
 - Expanded lipid panel;
 - Immunogenicity; and
 - Exploratory lipid and CV risk biomarkers;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Perform 12-lead ECG;
- Assess AEs;
- No study drug will be administered, and patients will be told to continue oral lipid lowering medications. Patients entering the long-term OLE study with LIB003 must review and sign an informed consent form (ICF) before being dosed with LIB003 in the OLE protocol LIB003-007; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

6.2.10 Follow-Up Visit for Positive Anti-Drug Antibodies/Neutralizing Antibodies

Patients on LIB003 who test positive for binding, non-NAbs and have clinical sequelae that are considered safety related at the final visit (Day 169/Week 24/ET) may be asked to return for additional Q4W (≤ 31 days) follow-up testing if they terminated the base study (LIB003-004) and do not enter the OLE study.

Patients on LIB003 with positive NAb at the final visit (Day 169/Week 24/ET), who do not enter the OLE study and have no clinical sequelae, will be asked to return for follow-up testing every 3 months until either NAb are no longer detectable, considered stable or the patient has been followed for a period of at least 12 months. For patients who test positive, but have not received active drug, follow-up testing will not be required.

The following procedures will be performed at these follow-up visits:

- Record prior and concomitant medications, including statin, statin dose, ezetimibe, and other lipid lowering medications plus adherence for prior 4 weeks;
- Obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect fasting blood samples for the following:
 - Full safety chemistry panel and hematology;
 - PK;
 - PCSK9 (free);
 - Brief lipid panel; and
 - Immunogenicity sample;
- Assess injection site;
- Assess AEs; and
- Remind patient the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet.

7 PHARMACODYNAMIC AND PHARMACOKINETIC ASSESSMENTS

Blood samples for PK and PD assessments will be collected at designated study visits specified in [Appendix A](#).

All blood samples should be collected while the patient is in a fasted state (≥ 10 hours; ad libitum water is permitted and encouraged), prior to administration of study drug (LIB003 or placebo), and, where feasible, prior to completing other visit assessments, with the exception of body weight. After the scheduled analyses are completed, residual samples may be utilized for further exploratory analyses. Instructions for specimen collection and storage are detailed in the laboratory manual.

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

7.1 Pharmacodynamic Assessments

LDL-C (calculated by Friedewald and Hopkins formulas, and measured by preparative ultracentrifugation) TC, HDL-C, non-HDL-C, VLDL-C, TG, apo B, and Lp(a) will be measured in all patients. Serum (free) PCSK9 concentrations will be measured at designated visits in LIB003 patients, with samples at interim visits measured in response to immunogenicity ([Section 8.10](#)). Samples from placebo patients will be stored for potential future assessment.

7.2 Pharmacokinetic Assessments

The PK concentration for LIB003 will be initially measured at designated visits in LIB003 patients, with samples at interim visits measured in response to the population pharmacokinetic plan or immunogenicity ([Section 8.10](#)). Samples from placebo patients will be stored for potential future assessment.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

An AE 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 AE 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 AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time of signing informed consent until study participation is complete. Patients should be instructed to report any AE that they experience to the Investigator. From the time following the first dose of study drug, the Investigator should make an assessment for AEs at each visit and record the event on the appropriate AE 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 AE 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 AE, not the procedure.

Any medical condition already present at the time of the first dose of study drug should not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

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 AEs, as described below. 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 result that is determined to be an error does not require reporting as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE 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; and/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 AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For LIB003, the reference safety information for the purposes of expedited reporting is included in Section 6 of the Investigator's Brochure. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE 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 AE 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 AE 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 AE 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 administered. 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.

8.1.4 Adverse Event of Special Interest

The Investigator will monitor each subject for clinical and laboratory evidence for pre-defined adverse events of special interest (AESIs) throughout the subject's participation in this study.

The Investigator will assess and record any additional information on the AESI in detail on an adverse event form which must be submitted within 24 hours of awareness of the event.

For this study, AESIs include the following:

- Confirmed ALT or AST levels $>3 \times \text{ULN}$; and
- Confirmed CK levels $> 10 \times \text{ULN}$ with muscle pain, tenderness or weakness.

During the course of the study, additional AESIs may be identified by the Sponsor.

Adverse events of special interest must be recorded in the eCRF.

8.2 Serious Adverse Events

An AE 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 AE;
 - Note: An AE 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 AEs 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, respite care) 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 1 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 final visit (Week 24) 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 AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the reporting period must be reported.

Any SAE, regardless of expectedness or causality, should be reported by completing the AE 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 the EDC system 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 +1-513-579-9911, dial 3

Fax: +1-866-336-5320 or +1-513-570-5196

e-mail: medpace-safetynotification@medpace.com

Medpace SAE reporting line – Europe:

Telephone: +49 89 89 55 718 44

Fax: +49 89 89 55 718 104

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 a 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 who becomes pregnant while on study drug will immediately be withdrawn from the study and ET 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 applicable competent authorities in all countries concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and 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 applicable competent authorities in all countries concerned, and to the Central Ethics Committee, as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

Expedited reporting of suspected unexpected serious adverse reactions related to inclusion criteria required lipid lowering therapy (considered non-investigational medical products is not required). Listings of cases related to required lipid lowering therapy will be included in the Development Safety Update Report.

The Sponsor will also inform all Investigators as required.

8.6 Special Situation Reports

Special situation reports include reports of overdose, medication error:

- **Overdose:** refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied.
- **Medication Error:** Medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product by a healthcare professional. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of patients missing doses of study drug are not considered reportable as medication error.

- All special situation events as described above must be reported on the Special Situations Report form and faxed/mailed to Medpace Clinical Safety (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management and outcome should be provided, when available.

8.7 Data Safety Monitoring Board

In addition to ongoing safety monitoring by the Medical Monitor and clinical staff, a formally constituted and chartered DSMB will monitor safety, including all-cause mortality, CVE and immunogenicity (ADAs, NABs, and any related clinical and PD effects) over the course of the study. As outlined below, the CVEs will be adjudicated by a blinded independent committee at an academic institution and provided to the DSMB on a regular basis. The DSMB will consist of external physicians and a biostatistician. It is anticipated that the DSMB will have regular meetings, once every 3 to 6 months, depending on study enrollment rate. Ad hoc meetings may be scheduled if unanticipated safety events occur. After review of data at each meeting, the DSMB will make recommendations about further conduct of the study.

8.8 Cardiovascular Events

CVEs and all deaths will be collected post-randomization in this study. CVEs will include, but are not limited to, the following: CV death, non-fatal MI, stroke (non-fatal ischemic, hemorrhagic, and undetermined) and TIAs, urgent coronary revascularization and unstable angina, new onset peripheral vascular disease (PVD) or revascularization for PVD. All-cause mortality will be assessed.

8.8.1 Clinical Endpoint Committee

A Clinical Endpoint Committee (CEC) will review and adjudicate CVEs for the full program. CVEs reported during telephone contacts will also be adjudicated. The CEC will be comprised of qualified judges, who are not Investigators in the study and not otherwise directly associated with the Sponsor. The CEC judges will remain blinded to treatment throughout the adjudication process for the double-blind study and unblinded for the OLE study. The CEC will follow its own charter for processing and adjudicating CVEs. As this is a double-blind study, all members of the adjudication committee will be blinded as to the treatment group for each patient – either LIB003 or placebo. The CEC will complete assessments on an ongoing basis, and all information will be recorded in a database. Adjudication of events will be based on evaluation of eCRFs and source documents including but not limited to available hospital discharge summaries, autopsy reports, consultation papers, x-rays/scanning reports and laboratory reports.

More information on the definition of each component of CVEs and on the CEC will be included in the CVE adjudication charter.

8.9 Clinical Laboratory Evaluations

Clinical laboratory profiles for lipids, hematology, serum safety chemistry, and urinalysis will be evaluated from samples collected after ≥ 10 hours of fasting (ad libitum water is permitted and encouraged) at designated study visits specified in [Appendix A](#). The study is double-blind with study staff (not involved with drug administration), Investigators, and patients blinded to study

drug (LIB003 or placebo) assignments. To maintain the blind all lipid, PK, and PCSK9 measurements after Day 1 will remain blinded to Investigators, study staff, and patients until completion of the full study.

For all females of childbearing potential, a urine pregnancy test will be performed at screening and the end of study visit (Week 24/ET). Serum FSH will be measured for women uncertain of postmenopausal status (<1 year since last menses) at screening only.

TSH will be measured in all patients; patients with TSH <LLN or $>1.5 \times$ ULN will have a free T3 (FT3) performed. HbA1c will be measured at Day 1 and the end of study visit (Week 24/ET).

PK (LIB003) samples will be collected for all patients at all Q4W visits but will be measured in only those patients who received LIB003. Initially, only samples at Weeks 12 and 24 will be measured to support the population pharmacokinetics plan with additional visits analyzed to support immunogenicity dependent on the results at Weeks 12 and 24 (Section 8.10).

PCSK9 (free) samples will be collected for all patients at every Q4W visits but will be measured in only those patients who received LIB003. Initially only samples at Day 1, Week 12 and Week 24 measured. Additional visits will be analyzed to support immunogenicity (Section 8.10). Samples from placebo patients will be stored for potential future assessment.

A complete list of the clinical laboratory analytes is included in [Appendix B](#).

8.9.1 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 DILI events that meet the following criteria must be reported as SAEs ([Section 8.3](#)):

- ALT or AST levels $>3 \times$ ULN;
- Total bilirubin levels $>2 \times$ ULN, without initial findings of Gilbert's syndrome or cholestasis (elevated serum alkaline phosphatase); and
- 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.

8.10 Immunogenicity

Serum will be collected for immunogenicity (ADAs) at all Q4W (≤ 31 days) visits for all patients, ADAs will be initially analyzed for LIB003 patients at Day 1, Week 12 and Week 24/ET ([Appendix A](#)). Patients confirmed positive for LIB003 antibodies at Week 12 or Week 24/ET will be tested for NAbs, including PK and PCSK9, at that visit. Previous visit samples may be analyzed as outlined above in order to better characterize the findings. ADAs may be further characterized for isotype, binding site, and affinity. Samples collected for placebo-treated patients will be stored for potential measurement.

In addition to proscribed immunogenicity testing described, blinded safety, ISR, and lipid data will be reviewed by the DSMB at pre-determined intervals throughout the program. If indicated by these assessments, ADAs will be analyzed during study conduct to support safety monitoring. Patients with confirmed positive ADA titers will have neutralizing antibodies (NAbs), PK

(LIB003), and free PCSK9 assessed. DSMB will also assess impact of ADA on attenuating efficacy of free PCSK9 suppression and LDL-C reduction.

Patients on LIB003 who test positive for binding, non-NABs and have clinical sequelae that are considered safety-related at the final visit of this study (Week 24/ET) may be asked to return for additional monthly follow-up testing if they terminate LIB003-004 and do not enter the OLE study.

Patients on LIB003 who test positive for NABs at the final visit of this study (Week 24/ET), who do not enter the OLE study, and have no clinical sequelae, will be asked to return for follow-up testing every 3 months until either NABs are no longer detectable, considered stable or the patient has been followed for a period of at least 12 months. For patients who test positive, but have not received active drug, follow-up testing will not be required.

8.11 Vital Signs

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

8.12 Electrocardiograms

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

8.13 Physical Examinations

Physical examinations and injection site assessments will be performed at designated study visits specified in [Appendix A](#).

Body weight will be obtained at designated study visits specified in [Appendix A](#). Height will be obtained only at screening and used to calculate BMI.

8.14 Genetic Testing

Peripheral blood cell DNA for determination of HeFH variants will be collected at the randomization visit (Day1) and will be analyzed as necessary.

This data will be used to assess genetic versus clinical diagnosis, categorize receptor function and assess response based on FH variants.

8.15 Reserve Exploratory Biomarker Samples

Additional reserve blood samples will be collected at Day 1 and Week 24/ET, to be available for analysis of lipid and CV risk exploratory biomarkers and/or repeat or additional clinical laboratory testing in the event of a safety issue.

Reserve samples will be stored for a minimum of 1 year following study completion and may be stored until the investigational new drug application is withdrawn or the new biologics license application or marketing authorization application is approved. If requested, results of tests performed on study samples will be made available to patients or Investigators. Patients may not withdraw their samples.

9 STATISTICS

The statistical analysis will be carried out as specified in the Statistical Analysis Plan which will be finalized before database lock and is briefly summarized below.

9.1 Analysis Populations

The Intent-to-Treat (ITT) Population is defined as all patients who are eligible and randomized into the study. The primary efficacy endpoint will be analyzed with the ITT Population.

The modified Intent-to-Treat (mITT) Population is defined as all ITT patients who have LDL-C measurements at Week 24. The primary efficacy analysis will be repeated on the mITT Population to test the robustness.

The Per Protocol Population is defined as all mITT patients who receive all doses of study drug, have valid Week 24 LDL-C measurements, and have no major protocol deviations during the Treatment Period. If the drug dosing period from the prior dose is more than 31 days, then this LDL-C measurement will not be considered as valid.

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

9.2 Statistical Methods

The study baseline for all efficacy analyses is defined as the valid measurement on Day 1. If the measurement at this visit is missing, the last measurement prior to the first dose of study drug will be used.

9.2.1 Efficacy Analysis

The coprimary efficacy endpoints are to assess percent change from baseline compared to placebo in LDL-C level at Week 24 (by Friedewald formula) and LDL-C level at the mean of Weeks 22 and 24 (by Friedewald formula). Percent change from baseline in LDL-C will be analyzed with analysis of covariance model with treatment as a factor and baseline value as a covariate. For patients in the ITT Population who withdraw early, a multiple imputation will be used to explore the potential impact of missing data. For analysis of each primary objective, the treatment comparison will use a significance level of 0.05.

Other efficacy variables will be analyzed similarly. Multiplicity adjustment will be based on a combination of sequential testing, the Hochberg procedure, and fallback procedure to control the overall significance level for the primary and all secondary endpoints. A sensitivity analysis of the coprimary endpoints will be done by application of a mixed-effect model repeat measurement and rank analysis of covariance (Quade test) for patients who adhered to the scheduled study drug administration with visits ≤ 31 days and did not have any missing data for the coprimary endpoints. A post-hoc exploratory subgroup analysis will be performed on the percentage change from baseline in LDL cholesterol and other lipid parameters by genotype status (confirmed or unconfirmed) and by LDL receptor, apo B or PCSK9 variant status. The data will be analyzed using a mixed-effect model repeated measurement with terms for baseline, treatment group, scheduled visit, and the interaction of treatment and scheduled visit. The estimate the mean treatment effect differences and 95% CIs between subgroups will be determined.

9.2.2 Pharmacodynamic Analysis

PD analysis will be performed based on the ITT Population. PD and exploratory endpoints will be summarized at each visit, as well as percent change or change from baseline compared to placebo. Inferential analysis may be performed if the data permit.

Free serum PCSK9 concentrations will be assessed for all LIB003 patients at Day 1, Week 12, and Week 24. Additional timepoints may be analyzed for patients in support of ADAs.

9.2.3 Immunogenicity Analysis

Immunogenicity data will be listed. ADA data will initially be analyzed for all LIB003 patients at Day 1, Week 12 and Week 24/ET. Additional timepoints will be analyzed for those patients confirmed ADA positive at Week 24/ET.

9.2.4 Pharmacokinetic Analysis

PK will be summarized for all LIB003 patients at Week 12 and Week 24/ET. Additional PK timepoints may also be summarized to support the population pharmacokinetic plan or in support of ADAs.

9.2.5 Safety Analysis

The safety endpoint data will be summarized for the Safety Population. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. A general summary of the AEs and SAEs will be summarized by overall number of AEs, severity, and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of AEs will be summarized by system organ class, preferred term, and treatment group. For AEs and SAEs of special interest, a risk difference along with the 95% CI will be used to compare the treatment groups.

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

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

Deaths and CVEs will be collected and will be adjudicated by an independent CEC. Events that are adjudicated as a "CVE" will be listed and summarized in the current study. In addition, all Phase 3 studies will collect CVEs, and a summarization by treatment group will be performed on the integrated (across all Phase 3 studies) data. Additional details regarding the CV-specific events and their definitions will be included in the CVE adjudication charter.

9.2.6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

9.2.7 Interim Analysis

No interim analysis is planned for this study.

9.2.8 Sample Size Determination

The number of patients is based on administration of LIB003 300 mg Q4W (≤ 31 days) achieving at least 95% power to detect a statistically significant difference in LDL-C level at both Week 24 and at the mean of Weeks 22 and 24 compared to the placebo group at 2-sided alpha level of 0.05, assuming a common standard deviation of 17.5% for percent change in LDL-C and a treatment difference of 50%, as determined by literature review. In terms of safety, while the number of patients is not based on statistical consideration, there is an 80% probability of observing at least 1 occurrence in an LIB003 treatment group of any AE which would occur with a 24% incidence in the population from which the sample is drawn. Approximately 600 patients will participate in this clinical study, including 400 to receive LIB003 and 200 to receive placebo.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRAs will verify data recorded in the 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 have 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 username 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) (ie, 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 will be used for medical history and AEs. The latest version 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.

10.3 End of Study

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study. Patients successfully completing the study may enter into a separate long-term follow-up study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients 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/Independent Ethics Committee

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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/IEC approval has been obtained. The protocol, Investigator's Brochure, 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/IEC by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB/IEC 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/IEC.

No drug will be released to the site for dosing until written IRB/IEC 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/IEC 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 patient to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC, 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 are 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 Food and Drug Administration, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC 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/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

13 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES

	Screening Period					Double-Blind Treatment Period									Follow-Up Visit [4]
	Randomization Ready [2]		Diet/Lipid Stabilization (With Washout and/or Stabilization) [3]												
Study Procedure Day (Visit Window [Days])	-21 to -5		-77 to -5			1[5]	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	155 (±3)	169/ET (±3)		
Visit (Week)	Screening	RL [6]	Screening	EL [7]	RL[6]	W0	W4	W8	W12	W16	W20	W22	W24		
Informed consent	X		X												
Meets clinical or genetic criteria for HeFH	X		X												
Demographics	X		X												
Medical history	X		X			X									
PCSK9 mAb washout [3]			X												
Inclusion/exclusion criteria	X	X	X	X	X	X [8]									
Prior/concomitant meds [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DNA/genotyping for HeFH [10]						X									
TSH [11]	X		X												
Pregnancy/FSH test [12]	X	X	X		X								X		
Full safety chemistry panel	X		X			X		X					X	X	
Brief safety chemistry panel							X		X	X	X				
Hematology and urinalysis	X		X			X							X	X	
HbA1c						X							X		
Brief lipid panel	X	X	X	X	X		X	X	X	X	X	X		X	
Expanded lipid panel						X							X		
PK blood sample (LIB003 patients only) [13]							X	X	X [14]	X	X		X [14]	X	
PCSK9 measurement[13]						X [14]	X	X	X [14]	X	X		X [14]	X	

	Screening Period					Double-Blind Treatment Period									Follow-Up Visit [4]
	Randomization Ready [2]		Diet/Lipid Stabilization (With Washout and/or Stabilization) [3]												
Study Procedure Day (Visit Window [Days])	-21 to -5		-77 to -5			1[5]	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	155 (±3)	169/ET (±3)		
Visit (Week)	Screening	RL [6]	Screening	EL [7]	RL[6]	W0	W4	W8	W12	W16	W20	W22	W24		
Immunogenicity assessment [13]						X [14]	X	X	X[13]	X	X		X [14]	X	
Exploratory lipid and CV risk biomarkers [15]						X							X		
Body weight [16]	X		X			X				X			X	X	
Height [16]	X		X												
Vital signs [17]	X		X			X	X	X	X	X	X	X	X	X	
Physical examination	X		X							X					
12-lead ECG [18]	X		X			X							X		
Randomization						X									
Study drug administration						X	X	X	X	X	X				
Injection site assessment [19]						X	X	X	X	X	X				
Patient counseling [20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events						X	X	X	X	X	X	X	X	X	

A ±3-day window is permitted for all clinic visits, but **every attempt should be made to dose patients ≤31 days from prior dose** (not from Day 1); unanticipated or unavoidable cancellations due to weather or public holidays may be scheduled within a 5-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 permitted and encouraged), prior to administration of study drug (LIB003 or placebo), and, where feasible, prior to completing other visit assessments, with the exception of body weight.

See [Appendix B](#) for a complete list of safety chemistry, lipid, hematology, and urinalysis analytes.

- These visits are only for patients who do not require washout and/or diet and lipid stabilization. Screening procedures must be performed no earlier than 5 days and no later than 21 days prior to commencing randomization and dosing on Day 1. Patients documented to have been on allowed oral lipid-lowering medication for ≥4 weeks and who have not received any PCSK9 mAb for the period specified in the inclusion/exclusion criteria (which is dependent on dose of mAb at screening) may proceed directly to randomization on Day 1.
- These visits are only for patients who do require washout and/or diet and lipid stabilization. Screening procedures must be performed no earlier than 5 days and no later than 77 days prior to commencing randomization and dosing on Day 1. For patients on a PCSK9 mAb at a dose of 75 mg, 140 mg, or 150 mg Q2W, the washout period is ≥4 weeks after the last dose, and for those on 300 mg or 420 mg Q4W (≤31 days) the washout period is ≥8 weeks following last dose (see inclusion/exclusion criteria in [Section 4](#)). For patients who have received an siRNA PCSK9 inhibitor, the washout period is ≥360 days post last dose. During the washout phase patients may have up to 2 additional clinic visits for assessment of inclusion/exclusion criteria.

3. Patients on LIB003 who test positive for binding, non-NABs and have clinical sequelae that are considered safety-related at the final visit of this study (Day 169/Week 24/ET) may be asked to return for additional monthly follow-up testing if they terminate this study (LIB003-004) and do not enter the OLE study. Patients on LIB003 who test positive for NABs at the final visit of this study (Day 169/Week 24/ET), who do not enter the OLE study, and have no clinical sequelae, will be asked to return for follow-up testing every 3 months until either NABs are no longer detectable, considered stable, or the patient has been followed for a period of at least 12 months. For patients who test positive, but have not received active drug, follow-up testing will not be required.
4. The Investigator and Sponsor will receive lipid, PK and PCSK9 baseline measurements for Day 1. Measurements after Day 1 will be blinded to the Investigator and study personnel involved in the study at both the clinical site and LIB Therapeutics.
5. Patients whose LDL-C is up to 5 mg/dL below the defined entry level based on very-high risk for CVD or high risk for CVD or triglycerides >400 to 450 mg/dL may have 1 fasting lipid repeat profile (Screening Visit repeat lipid [RL]).
6. Patients who meet HeFH and other entry criteria but require washout of lipid-lowering agents excluded in the study (see inclusion/exclusion criteria in [Section 4](#)) and/or diet and allowed oral lipid-lowering drug stabilization (eg, statins, ezetimibe, bile acid sequestrants, OM-3, bezafibrate, fenofibrate, nicotinic acid, and bempedoic acid) will have a fasting lipid profile at the EL Visit to determine the final eligibility after completing the required washout/stabilization period.
7. Review inclusion and exclusion criteria.
8. Includes statin, statin dose, ezetimibe, and other oral lipid-lowering medications (bile acid sequestrants, nicotinic acid, bezafibrate, fenofibrate, OM-3 compounds, and bempedoic acid) plus adherence for 4 weeks; record prior treatment with evolocumab or alirocumab including dose, dosing frequency, and last dose. For Day 1/Week 0 verify the last dose of a PCSK9 mAb was ≥ 4 to 8 weeks ago.
9. Blood sample for DNA/genotyping of HeFH will be obtained at the randomization visit, if necessary.
10. TSH at screening. For patients with TSH <LLN or $>1.5 \times$ ULN an FT3 will be performed.
11. A urine pregnancy test will be performed only on females of childbearing potential. Serum FSH will be measured for women uncertain of postmenopausal status (<1 year since last menses) at screening only.
12. Serum will be collected for immunogenicity (ADAs), PCSK9, and PK at all Q4W visits for all patients. ADAs will be analyzed initially for LIB003 patients at Day 1 and Weeks 12 and Week 24/ET. PK will be analyzed at Weeks 12 and 24/ET and PCSK9 will be analyzed at Day 1 and Weeks 12 and 24/ET. Patients confirmed positive for LIB003 antibodies at Week 12 or Week 24/ET will be tested for NABs, PCSK9 (free), and PK at that visit. Previous visit samples may be analyzed as outlined above (immunogenicity, PCSK9, and PK) to better characterize the findings. Samples collected for placebo-treated patients will be stored for potential measurement.
13. Measured initially. Other time points analyzed to address positive ADAs or population PK plan (PK only).
14. Blood samples for exploratory biomarkers will be collected and frozen for potential assessment of additional lipid or CV risk biomarkers.
15. Height and body weight will be used to calculate BMI. BMI will be calculated only at screening.
16. Includes 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.
17. Patients should be resting in the supine position for ≥ 10 minutes prior to each 12-lead ECG.
18. On Day 1 and subsequent visits injection site assessments will be performed pre-dose and 15 minutes post-dose.
19. Patients will be reminded at all visits as to the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet. Patients will be reminded at visits from Week 0 to Week 16 the importance of returning to the clinic in 28 days (≤ 31 days) for next dose of study drug. Patients will be reminded at Week 20 and Week 22 visits the importance of returning to the clinic in 14 days for the Week 22 and Week 24 visits, respectively.

ADA = anti-drug antibody; BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EL = eligibility lipid; ET = Early Termination; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; HbA1c = glycated hemoglobin; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLN = lower limit of normal; mAb = monoclonal antibody; meds = medications; NAB = neutralizing antibody; OLE = open-label extension; OM-3 = omega-3 fatty acids; PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W (≤ 31 days) = monthly; RL = repeat lipid; siRNA = short interfering ribonucleic acid; TG = triglycerides; TSH = thyroid stimulating hormone; ULN = upper limit of normal; W = week.

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
Low-density lipoprotein cholesterol [1]
Non– high-density lipoprotein cholesterol (Total cholesterol minus high-density lipoprotein cholesterol)
Cholesterol
Triglycerides

1. Low-density lipoprotein cholesterol will be calculated by Friedewald and Hopkins formulae.

Expanded Fasting Lipid Panel

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

Endocrinology

Urine pregnancy test for females of childbearing potential

Serum follicle-stimulating hormone for women uncertain of postmenopausal status
(<1 year since last menses)

Thyroid stimulating hormone for patients with thyroid stimulating hormone <LLN or >1.5
× ULN a free T3 (FT3) is performed

Hematology

Hematocrit

Hemoglobin

Platelets

Red blood cell count

White blood cell count and differential [1]

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

Glycated Hemoglobin (performed from hematology sample)

Urinalysis

Bilirubin

Glucose

Leukocyte esterase

Nitrite

Protein

Urobilinogen

Blood

Ketones

Microscopy [1]

pH

Specific gravity

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

PCSK9 (Free)

Pharmacokinetics (PK):

LIB003 concentrations

Immunogenicity:

Based on anti-drug (LIB003) antibody (ADA) results the following may also be measured:

Neutralizing antibodies

Exploratory Lipid and Cardiovascular Risk Biomarkers:

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

Deoxyribonucleic Acid:

Sample will be isolated from whole blood, stored. The need for the analysis of HeFH variants will be determined by clinical phenotype.

APPENDIX C: SIMON BROOME REGISTER CRITERIA

Simon Broome Diagnostic Criteria for Familial Hypercholesterolemia	
Point	Criteria
1	Total cholesterol levels >290 mg/dL (7.5 mmol/L) or LDL-C >190 mg/dL (4.9 mmol/L) in adults. Total cholesterol levels >260 mg/dL (6.7 mmol/L) or LDL-C >155 mg/dL (4.0 mmol/L)
2	Tendon xanthomas in the patient or tendon xanthomas in a first or second degree relative.
3	DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.
4	Family history of myocardial infarction before age 50 years in a second degree relative or before age 60 years in a first degree relative.
5	Family history of elevated total cholesterol >290 ml/dL (7.5 mmol/L) in an adult first or second-degree relative. Family history of elevated total cholesterol >260 ml/dL (6.7 mmol/L) in child, brother, or sister 16 years or younger.
Diagnosis	
Definite familial hypercholesterolemia = 1+2 or 3 Possible familial hypercholesterolemia = 1+4 or 5	
Apo = apolipoprotein; DNA = deoxyribonucleic acid; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Source: Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. <i>Am J Epidemiol.</i> 2004;160(5):407-420	

APPENDIX D: DUTCH LIPID CLINIC NETWORK CRITERIA

Criteria	Score
Family History	
First degree relative with known premature coronary and/or vascular disease (men aged <55 years, women aged <60 years) OR First degree relative with known LDL-C above the 95 th percentile for age and gender	1
First degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged <18 years with LDL-C above the 95 th percentile for age and gender	2
Clinical History	
Patients with premature coronary artery disease (men aged <55 years, women aged <60 years)	2
Patients with premature cerebral or peripheral vascular disease (men aged <55 years, women aged <60 years)	1
Physical Examination	
Tendinous xanthomata	6
Arcus cornealis before 45 years of age	4
LDL-C (mmol/L)	
≥8.5 (≥328 mg/dL)	8
6.5 – 8.4 (251 mg/dL – 327 mg/dL)	5
5.0 – 6.4 (193 mg/dL – 251 mg/dL)	3
4.0 – 4.9 (155 mg/dL – 192 mg/dL)	1
Diagnosis	Patient Total
Definite FH	>8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	<3
FH = familial hypercholesterolemia; LDL-C = low density lipoprotein cholesterol. Sources: Austin MA, Hutter CM, Zimmern RL, et al. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. <i>Am J Epidemiol.</i> 2004;160(5):407-420 Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. <i>Curr Opin Lipidol.</i> 2012;23(4):282-289 Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. <i>Eur Heart J.</i> 2013;34(45):3478-3490a	

APPENDIX E: DEFINITION OF VERY-HIGH OR HIGH-RISK FOR CARDIOVASCULAR DISEASE

Very-High Risk	People with any of the following: - Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multi-vessel coronary disease with 2 major epicardial arteries having >50% stenosis), or carotid ultrasound. - DM with target organ damage [1], or at least 3 major risk factors, or early onset of T1DM of long duration (>20 years). - Severe CKD (eGFR <30 mL/min/1.73 m²). - A calculated SCORE ≥10% for 10-year risk of fatal CVD. - FH with ASCVD or with another major risk factor.
High Risk	People with: - Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. - Patients with FH without other major risk factors. - Patients with DM without target organ damage [1], with DM duration ≥10 years or another additional risk factor. - Moderate CKD (eGFR 30-59 mL/min/1.73 m²). - A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

1. Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.
ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = LDL cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
Sources: Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139(25)