

# **CLINICAL STUDY PROTOCOL**

## **Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of LIB003 in Healthy Hypercholesterolemic Subjects and Patients with Hypercholesterolemia on Statin Therapy**

**Investigational Product:** LIB003

**Protocol Number:** LIB003-001 (amendment 1)

**IND Number:** 134579

### **Sponsor:**

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

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## SIGNATURE PAGE

**STUDY TITLE: Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of LIB003 in Healthy Hypercholesterolemic Subjects and Patients with Hypercholesterolemia on Statin Therapy**

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

Signature

Date

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

## INVESTIGATOR AGREEMENT

By signing below, I agree that:

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

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

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Investigator's Signature

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Date

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Investigator's Printed Name

## SYNOPSIS

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**TITLE:** Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of LIB003 in Healthy Hypercholesterolemic Subjects and Patients with Hypercholesterolemia on Statin Therapy

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**PROTOCOL NUMBER:** LIB003-001

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**INVESTIGATIONAL PRODUCT:** LIB003

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**PHASE:** 1

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

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### OBJECTIVES:

The primary objective of this study is to assess the safety and tolerability of single subcutaneous (SC) and single intravenous (IV) doses of LIB003 in healthy hypercholesterolemic subjects and patients with hypercholesterolemia on stable statin therapy.

The secondary objectives of this study are the following:

- To assess the pharmacodynamic (PD) effects of single SC and single IV doses of LIB003 on plasma unbound (free) proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations, total PCSK9, and serum LDL-C in healthy hypercholesterolemic subjects and patients with hypercholesterolemia on statin therapy;
  - To assess the effects of single SC and single IV doses of LIB003 on serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TG);
  - To assess the effects of single SC and single IV doses of LIB003 on apolipoprotein (apo) B, apo A1, and lipoprotein (a) (Lp[a]) serum concentrations;
  - To assess single-dose pharmacokinetics (PK) and dose proportionality of LIB003 following SC and IV administration;
  - To assess the absolute bioavailability of single SC doses of 300 mg and 600 mg of LIB003; and
  - To assess the frequency of anti-drug (anti-LIB003) antibodies (immunogenicity) following single SC and IV doses of LIB003.
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The exploratory objectives of this study are the following:

- To assess the effects of single SC and single IV doses of LIB003 on other lipid and cardiovascular risk biomarkers including, but not limited to, high-sensitivity C-reactive protein (hs-CRP), as appropriate; and
- To compare the PD effects of LIB003 in healthy hypercholesterolemic subjects and in patients with hypercholesterolemia on statin therapy.

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### **POPULATION:**

The population for Cohorts 1 to 7 of this study includes men and women who are  $\geq 18$  and  $\leq 70$  years of age and have a calculated LDL-C (Friedewald)  $\geq 100$  mg/dL and  $\leq 190$  mg/dL and TG  $\leq 250$  mg/dL who are not on a lipid-lowering therapy. The population for Cohorts 8 and 9 of this study includes men and women who are  $\geq 18$  and  $\leq 70$  years of age and have a calculated LDL-C (Friedewald)  $\geq 100$  mg/dL and TG  $\leq 250$  mg/dL who are on stable statin therapy.

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### **STUDY DESIGN AND DURATION:**

This is a randomized, double-blind, placebo-controlled, single ascending dose study. Approximately 63 healthy hypercholesterolemic men and women aged  $\geq 18$  to  $\leq 70$  years who fulfill the inclusion and exclusion criteria will be enrolled at 1 site in the United States. Eligible subjects will be admitted to the clinical research unit on Day -1, dosed on Day 1, furloughed on Day 4 (72 hours post-dose), and return for 8 outpatient visits through Day 43 (study discharge); subjects whose LDL-C levels have not returned to within 20% of baseline will continue to be monitored weekly and subjects with positive anti-drug (anti-LIB003) antibodies at Day 43 will continue to be monitored at 4 week intervals until resolved or until judged to be chronic or stable by the Investigator. There will be 9 separate and sequential dose cohorts (7 SC cohorts, 2 IV cohorts). The population in Cohorts 1 to 7 will include subjects with LDL-C levels  $\geq 100$  mg/dL and  $\leq 190$  mg/dL and TG levels  $\leq 250$  mg/dL who are not on a lipid-lowering therapy; Cohorts 8 and 9 will include subjects with LDL-C levels  $\geq 100$  mg/dL and TG levels  $\leq 250$  mg/dL who are on stable statin therapy.

Within each cohort, 7 subjects will be randomized in a 5:2 ratio to receive a single dose of LIB003 (n=5) or placebo (n=2) on Day 1. Cohorts 1 to 7 will receive LIB003 doses of 25 mg SC, 75 mg SC, 150 mg SC, 300 mg SC, 600 mg SC, 300 mg IV, and 600 mg IV, respectively. Dose escalation will be based on the Medical Monitor's assessment of safety and tolerability data (adverse events, physical examination findings, clinical laboratory results, vital signs, and electrocardiograms [ECGs]) through Day 8 for at least 5 subjects who received study drug. All cohorts will each first enroll a sentinel group of 3 subjects, of which 2 will receive LIB003 and 1 will receive placebo in a double-blind fashion. The remaining 4 subjects will only be dosed after the available Day 4 (72 hours post-dose) safety data from the sentinel subjects are assessed and deemed safe and tolerable by the Medical Monitor. Cohort 6 (300 mg IV) may enroll after 5 subjects in Cohort 4 (300 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Cohort 7 (600 mg IV) may enroll after 5 subjects in Cohort 5 (600 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Similarly, once the SC dose in Cohort 3 (150 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 8 (150 mg SC) can begin enrolling subjects on stable statin therapy.

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Likewise, once the SC dose in Cohort 4 (300 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 9 (300 mg SC) can begin enrolling subjects on stable statin therapy.

To reduce the risk that the maximum observed plasma concentration ( $C_{max}$ ) of LIB003 after IV administration will exceed the  $C_{max}$  that has been achieved in the supporting 4-week pivotal toxicity study in monkeys where LIB003 has been administered as bolus injection over 1 to 5 minutes, IV dosing in this study will occur as an infusion of LIB003 in normal saline over 20 minutes. If stopping rules limit the highest SC dose cohort to a dose lower than the planned IV dose, then the highest safely attained SC dose will be evaluated by the Investigator and the Medical Monitor as a potential dose for the single-dose IV cohort since exposures from an IV dose of LIB003 are expected to be higher than those from SC dosing, which has <100% bioavailability in nonclinical studies in monkeys.

Serial PK and PD samples (PCSK9 and lipid panel) will be collected at selected time points through Day 43 and at weekly intervals thereafter if LDL-C has not returned to within 20% of baseline. In addition, LDL-C and VLDL-C will be measured by preparative ultracentrifugation on specified days during the study. An aliquot of the screening lipid specimen will be saved for later analysis of exploratory biomarkers for those eligible subjects who enter the study. All lipid, PK and PCSK9 results from the baseline measurements on Day 1 onward will be blinded to the Investigator and all site and Sponsor personnel involved in the study. Final safety assessments will include adverse events and the results from physical examinations, ECGs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. Injection site reactions will be monitored by physical examination.

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#### **DOSAGE FORMS AND ROUTE OF ADMINISTRATION:**

In Cohorts 6 and 7, LIB003 300 mg and 600 mg or matching placebo will be administered as an IV infusion in normal saline over 20 minutes.

In all other cohorts, LIB003 (25 mg, 75 mg, 150 mg, 300 mg, and 600 mg) or matching placebo will be administered as an SC injection.

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#### **PHARMACOKINETIC VARIABLES**

Pharmacokinetic parameters for the SC dose cohorts will include maximum observed concentration ( $C_{max}$ ), time of maximum observed plasma concentration ( $T_{max}$ ), plasma elimination half-life (T-HALF), area under the plasma concentration-time curve (AUC) from time 0 to the time of last quantifiable plasma concentration ( $AUC_{0-t}$ ), AUC from time 0 extrapolated to infinite time ( $AUC_{inf}$ ), apparent total body clearance (CL/F), apparent volume of distribution ( $V_z/F$ ), and absolute bioavailability of total LIB003.

Pharmacokinetic parameters for the IV dose cohort will include  $C_{max}$ ,  $T_{max}$ , T-HALF,  $AUC_{0-t}$ ,  $AUC_{inf}$ , total body clearance, and volume of distribution.

Absolute bioavailability of LIB003 following SC administration will be assessed for the 300 mg and 600 mg doses since these are the doses common to both routes of administration.

Additional PK parameters may be calculated if deemed appropriate.

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### **PHARMACODYNAMIC VARIABLES:**

The PD parameters include changes in LDL-C, total and unbound (free) PCSK9 concentrations, serum lipids parameters (TC, HDL-C, VLDL-C, and TG), apo B, apo A1, and Lp(a).

Fasting hs-CRP and other exploratory parameters may also be assessed.

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### **SAFETY VARIABLES:**

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

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### **STATISTICAL ANALYSES:**

#### Pharmacokinetic Analyses:

Pharmacokinetic analysis will be performed based on the PK Evaluable Population, which is defined as all subjects with valid PK parameters ( $C_{max}$  and AUC). Power Law model will be used to assess the dose proportionality for Cohorts 1 to 5 (SC doses). Bioavailability analysis of log-transformed PK parameters will be performed for Cohorts 6 and 7 (IV doses) and corresponding SC dose cohorts with a 2-sample t-test. All PK parameters and PK concentrations will be summarized descriptively.

#### Pharmacodynamic Analyses:

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

#### Safety Analyses:

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

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

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

Immunogenicity data will be listed.

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**SAMPLE SIZE DETERMINATION:**

Although the number of subjects is not based on statistical power considerations, administration of LIB003 to 5 subjects in each cohort provides an 80% probability of observing at least 1 occurrence in that cohort of any adverse event which would occur with a 24% incidence in the population from which the sample is drawn. Approximately 63 subjects will participate in this clinical study, including 45 to receive LIB003 and 18 to receive placebo.

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**SITES:** 1 site in the United States

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**SPONSOR:**

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

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
ALT	Alanine transaminase
apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
AUC	Area under the curve
AUC <sub>0-t</sub>	Area under the plasma concentration-time curve from time 0 to the time of last quantifiable plasma concentration
AUC <sub>inf</sub>	Area under the plasma concentration-time curve from time 0 extrapolated to infinite time
Baseline LDL-C	The baseline LDL-C for determining continued weekly visits if LDL-C is >20% lower from baseline at Day 43 will be the lowest of the pre-dose Friedewald calculated LDL-C (i.e. screening, screening/Day-1, Day -1 or Day 1). As Friedewald underestimates LDL-C <70 mg/dL, post-dose LDL-C will be by ultracentrifugation if LDL-C by Friedewald is >20% lower than baseline
BMI	Body mass index
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CL	Total body clearance
CL/F	Apparent total body clearance
CK	Creatine kinase
C <sub>max</sub>	Maximum observed plasma concentration
CRA	Clinical Research Associate
DHA	Docosahexaenoic acid
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
Enrollment	The day subject signs informed consent and first procedure performed
EPA	Eicosapentaenoic acid
F	Absolute bioavailability of total LIB003
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDL-C	High-density lipoprotein cholesterol

Abbreviation	Definition
HSA	Human serum albumin
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IV	Intravenous
Lab manual	Manual provided by the central laboratory containing detailed information on blood volume, sample collection, processing, storage and delivery to the laboratory
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein (a)
mAb	Monoclonal antibody
MABEL	Minimum anticipated biological effect level
NOAEL	No-observed-adverse-effect level
Pharmacy manual	Manual provided by the sponsor or CRO containing detailed information on study drug (LIB003 and placebo), receipt and storage, preparation (SC & IV), and drug accountability
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcF	Fridericia's Correction Formula
Reserve subject	A subject whom meets enrollment criteria, qualifies for randomization and is admitted on Day -1 as potential subject for randomization on Day 1 if subject in a sentinel or other key group is found not suitable for randomization
SAD	Single ascending dose
SAE	Serious adverse event
SC	Subcutaneous
T-HALF	Terminal elimination half-life
TC	Total cholesterol
TDAR	T-cell-dependent antibody responses
TG	Triglycerides
T <sub>max</sub>	Time of maximum observed plasma concentration
TMDD	Target-mediated drug disposition
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
V <sub>z</sub>	Volume of distribution
V <sub>z</sub> /F	Apparent volume of distribution

## 1 INTRODUCTION AND BACKGROUND INFORMATION

Atherosclerotic cardiovascular disease (ASCVD) is the main cause of morbidity and mortality in industrialized countries and, despite progress in treatment, is projected to cause >22 million deaths over the next 15 years.<sup>1</sup> Low-density lipoprotein cholesterol (LDL-C) has been identified as one of the major, and easily modifiable, risk factors for atherosclerosis.<sup>2</sup> Significant ASCVD benefit has been achieved since the introduction of statin therapy to reduce LDL-C.<sup>2</sup> However, significant unmet medical need remains for additional LDL-C reduction in patients with existing ASCVD and those at increased cardiovascular risk, including patients unable to tolerate statins or effective doses of statins and those with more severe elevations of LDL-C, such as those with familial hypercholesterolemia (FH).<sup>3</sup> Data from the Cholesterol Treatment Trialists' Collaboration has provided evidence that for every 1 mmol/L (~39 mg/dL) reduction in LDL-C, the risk of major cardiovascular events is reduced by 24%, although these data were collected mostly with statins.<sup>2</sup> The recent cardiovascular outcome study with the proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody (mAb), evolocumab (Repatha<sup>®</sup>), the FOURIER study, has confirmed this relationship for non-statin-lowering of LDL-C.<sup>4</sup> Furthermore, recent data from a number of studies, including post hoc analysis of the IMPROVE-IT and Phase 3 alirocumab (Praluent<sup>®</sup>) studies, plus the FOURIER and SPIRE (Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients) studies, have shown that the relationship between absolute LDL-C reduction and ASCVD event reduction remains linear and extends to very low LDL-C levels of <25 mg/dL without signals of adverse events either from PCSK9 inhibition or very low LDL-C.<sup>5,6,7,8,9</sup>

Proprotein convertase subtilisin/kexin type 9 is a circulating protein secreted mainly by the liver that plays a significant role in the recycling of hepatic low-density lipoprotein receptors (LDLRs) and has been identified as a validated drug target for reduction of LDL-C. The LDLR is the primary pathway for LDL-C elimination from circulation; plasma PCSK9 binds to the hepatic LDLR along with LDL-C, targeting the receptor for degradation after endocytosis and thus reducing the expression of LDLRs available to remove LDL-C from circulation. Gain-of-function mutations of PCSK9 are associated with elevated LDL-C and constitute a third cause of FH and accelerated ASCVD, while loss-of-function mutations of PCSK9 are associated with reduced levels of LDL-C and reductions in ASCVD.<sup>4,10,11,12</sup> Adverse effects or other metabolic disturbances have not been observed in subjects carrying loss-of-function PCSK9 mutations, even in a compound heterozygote with no detectable PCSK9 levels and strikingly low LDL-C (14 mg/dL), although recent Mendelian randomization studies have suggested the potential for increased diabetes in patients with impaired glucose tolerance or metabolic syndrome similar to that seen with statins.<sup>10,13,14</sup> Nonclinical studies in PCSK9 knockout or overexpressing mice revealed phenotypes consistent with the human clinical data.<sup>15</sup> Together, the clinical and nonclinical data for the PCSK9 mechanism of action provide a strong genetic proof of concept for targeting PCSK9 to reduce plasma LDL-C levels and lower the risk of coronary heart disease. Based on these observations, PCSK9 inhibition is a promising target for developing new non-monoclonal antibody therapies for reduction of plasma cholesterol levels.

LIB Therapeutics has developed LIB003, a Chinese hamster ovary-S-derived recombinant fusion protein therapeutic agent consisting of a PCSK9-binding domain and human serum albumin (HSA). The HSA contains an alanine substituted for the naturally occurring cysteine at residue 34. The PCSK9-binding domain (Adnectin) in LIB003 is derived from the 10<sup>th</sup> type III domain of human fibronectin (<sup>10</sup>F<sub>n</sub>3) modified by messenger ribonucleic acid display technology to bind

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

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

In this current study, inhibition of PCSK9 is not expected to adversely impact the cardiovascular system since both PCSK9-null mice and compound heterozygous humans with PCSK9 loss-of-function mutations exhibit no discernable cardiovascular phenotype.<sup>19,20,21</sup> Moreover, extensive clinical studies inhibiting PCSK9 with monoclonal antibodies have shown only cardiovascular benefit.<sup>4,5,6,7,8,9,18,19,20</sup> Evaluation of the effect of LIB003 on the cardiovascular, central nervous, and respiratory systems were included as part of the pivotal 4-week GLP toxicity study in cynomolgus monkeys in accordance with ICH S6 and S7 guidances.<sup>16</sup> Results from the study revealed that repeated administration of LIB003 had no effect on cardiovascular, central nervous system, and 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.

## 1.1 Rationale

This current first-in-human study of LIB003 is designed as a single ascending dose (SAD) study to assess single SC and IV doses. Additionally, the proposed study will evaluate the pharmacokinetic (PK) profile and pharmacodynamic (PD) effects following single dose administration of LIB003. To ensure that risks to subjects are minimized, subjects will be enrolled into the study in separate cohorts of 7 subjects each: 5 SC doses will be explored in subjects with LDL-C levels  $\geq 100$  and  $\leq 190$  mg/dL who are not receiving lipid-lowering treatment, of which the highest 2 SC doses will also be assessed as IV doses. Two SC doses will also be explored in subjects with LDL-C  $\geq 100$  mg/dL who are on stable statin therapy. The enrollment of all of these subjects will support the initial assessment of safety, tolerability, and PD effects in a population with key characteristics of the target patient population. Their inclusion in this study will further enable the comparison of the PD effects of LIB003 in a statin-naïve and in a statin-treated population. Safety and PD data derived from the statin-treated subjects will support the enrollment of these subjects and dose selection in subsequent studies.

## **1.2 Risk/Benefit**

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

While the clinical pharmacology and safety profile of LIB003 is not known, a directly-related Adnectin protein, LIB001 (BMS-962476) with an identical PCSK9-binding site and mechanism of action, was shown to reduce LDL-C levels both nonclinically and clinically and was safe and well tolerated in a Phase 1a clinical study. LIB003 has been well tolerated in nonclinical studies, and the studies conducted to date have demonstrated an acceptable safety profile for LIB003 to support the initiation of this Phase 1 clinical. Therefore, the risk to subjects in this study is considered low.

## **2 STUDY OBJECTIVES**

### **2.1 Primary Objective**

The primary objective of this study is to assess the safety and tolerability of single SC and single IV doses of LIB003 in healthy hypercholesterolemic subjects and patients with hypercholesterolemia on stable statin therapy.

### **2.2 Secondary Objectives**

The secondary objectives of this study are the following:

- To assess the PD effects of single SC and single IV doses of LIB003 on plasma unbound (free) PCSK9 concentrations, total PCSK9, and serum LDL-C in healthy hypercholesterolemic subjects and patients with hypercholesterolemia on statin therapy;
- To assess the effects of single SC and single IV doses of LIB003 on serum lipids, including TC, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), and TG;
- To assess the effects of single SC and single IV doses of LIB003 on apo B, apo A1, and Lp(a) serum concentrations;
- To assess single-dose PK and dose proportionality of LIB003 following SC and IV administration;
- To assess the absolute bioavailability of single SC doses of 300 mg and 600 mg of LIB003; and
- To assess the frequency of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) following single SC and IV doses of LIB003.

### **2.3 Exploratory Objectives**

The exploratory objectives of this study are the following:

- To assess the effects of single SC and single IV doses of LIB003 on other lipid and cardiovascular risk biomarkers including, but not limited to, high-sensitivity C-reactive protein (hs-CRP), as appropriate; and
- To compare the PD effects of LIB003 in healthy hypercholesterolemic subjects and in patients with hypercholesterolemia on statin therapy.

### 3 STUDY DESCRIPTION

#### 3.1 Summary of Study Design

This is a randomized, double-blind, placebo-controlled, single ascending dose study. Approximately 63 healthy hypercholesterolemic men and women aged  $\geq 18$  to  $\leq 70$  years who fulfill the inclusion and exclusion criteria will be enrolled at 1 site in the United States. Eligible subjects will be admitted to the clinical research unit on Day -1, dosed on Day 1, furloughed on Day 4 (72 hours post-dose), and return for 8 outpatient visits through Day 43 (study discharge); subjects whose LDL-C levels have not returned to within 20% of baseline will continue to be monitored weekly. There will be 9 separate and sequential dose cohorts (7 SC cohorts, 2 IV cohorts). The population in Cohorts 1 to 7 will include subjects with LDL-C levels  $\geq 100$  mg/dL and  $\leq 190$  mg/dL and TG levels  $\leq 250$  mg/dL who are not on a lipid-lowering therapy; Cohorts 8 and 9 will include subjects with LDL-C levels  $\geq 100$  mg/dL and TG levels  $\leq 250$  mg/dL who are on stable statin therapy.

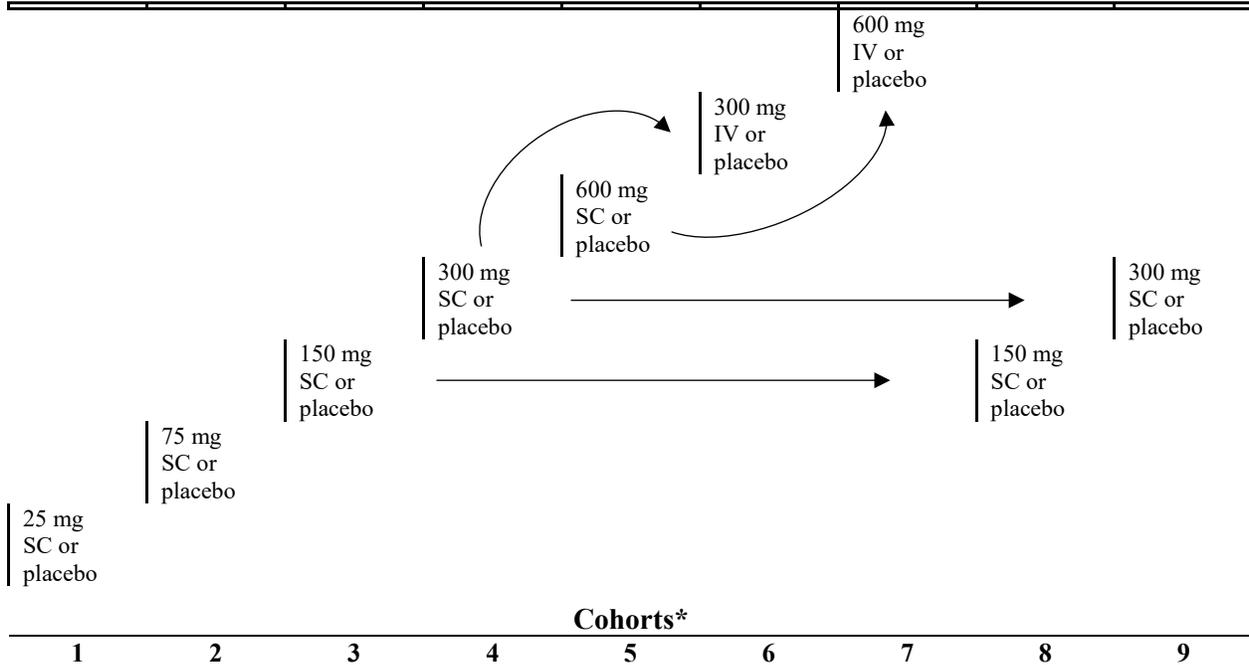
Within each cohort, 7 subjects will be randomized in a 5:2 ratio to receive a single dose of LIB003 (n=5) or placebo (n=2) on Day 1. Cohorts 1 to 7 will receive LIB003 doses of 25 mg SC, 75 mg SC, 150 mg SC, 300 mg SC, 600 mg SC, 300 mg IV, and 600 mg IV, respectively. Dose escalation will be based on the Medical Monitor's assessment of safety and tolerability data (adverse events, physical examination findings, clinical laboratory results, vital signs, and electrocardiograms [ECGs]) through Day 8 for at least 5 subjects who received study drug. All cohorts will each first enroll a sentinel group of 3 subjects, of which 2 will receive LIB003 and 1 will receive placebo in a double-blind fashion. The remaining 4 subjects will only be dosed after the available Day 3 (72 hours post-dose) safety data from the sentinel subjects are assessed and deemed safe and tolerable by the Medical Monitor. Cohort 6 (300 mg IV) may enroll after 5 subjects in Cohort 4 (300 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Cohort 7 (600 mg IV) may enroll after 5 subjects in Cohort 5 (600 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Similarly, once the SC dose in Cohort 3 (150 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 8 (150 mg SC) can begin enrolling subjects on stable statin therapy. Likewise, once the SC dose in Cohort 4 (300 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 9 (300 mg SC) can begin enrolling subjects on stable statin therapy. Figure 1 presents the study design schematic.

To reduce the risk that the maximum observed plasma concentration ( $C_{max}$ ) of LIB003 after IV administration will exceed the  $C_{max}$  that has been achieved in the supporting 4-week pivotal toxicity study in monkeys where LIB003 has been administered as bolus injection over 1 to 5 minutes, IV dosing in this study will occur as an infusion of LIB003 in normal saline over 20 minutes. If stopping rules limit the highest SC dose cohort to a dose lower than the planned IV dose, then the highest safely attained SC dose will be evaluated by the Investigator and the Medical Monitor as a potential dose for the single-dose IV cohort since exposures from an IV dose of LIB003 are expected to be higher than those from SC dosing, which has  $<100\%$  bioavailability in nonclinical studies in monkeys.

Serial PK and PD samples (PCSK9 and lipid panel) will be collected at selected time points through Day 43 and at weekly intervals thereafter if LDL-C has not returned to within 20% of baseline. In addition, LDL-C and VLDL-C will be measured by preparative ultracentrifugation on specified days during the study. An aliquot of the screening lipid specimen will be saved for later

analysis of exploratory biomarkers for those eligible subjects who enter the study. All lipid results from the baseline measurements on Day 1 onward will be blinded to the Investigator and all site and Sponsor personnel involved in the study. Final safety assessments will include adverse events and the results from physical examinations, ECGs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. Injection site reactions will be monitored by physical examination.

**Figure 1. LIB003 Single Ascending Dose Schedule – Day 1**



\*All cohorts will each first enroll a sentinel group of 3 subjects, of which 2 will receive LIB003 and 1 will receive placebo in a double-blind fashion.

Cohorts 1 to 7 will include subjects with calculated LDL-C (Friedewald) levels  $\geq 100$  mg/dL and  $\leq 190$  mg/dL and TG levels  $\leq 250$  mg/dL who are not on a lipid-lowering therapy.

Cohorts 8 and 9 will include subjects with calculated LDL-C (Friedewald) levels  $\geq 100$  mg/dL and TG levels  $\leq 250$  mg/dL who are on stable statin therapy.

IV = intravenous; LDL-C = low-density lipoprotein cholesterol; SC = subcutaneous; TG = triglycerides.

### 3.2 Stopping Rules

To ensure that risks to subjects are minimized, subjects will be enrolled into the study in separate cohorts of 7 subjects each. The first SC cohort and the IV cohort will each enroll a sentinel cohort of 3 subjects, of which 2 subjects will receive LIB003 and 1 will receive placebo in a double-blind fashion. The remaining 4 subjects will only be dosed after the available Day 3 (72 hours post-dose) safety data from the sentinel subjects are assessed and deemed safe and tolerable by the Medical Monitor.

Dose escalation will be based on the Medical Monitor's assessment of safety and tolerability data (adverse events, physical examination findings, clinical laboratory results, vital signs, and ECGs) through Day 8 for at least 5 subjects who received study drug. Cohort 6 (300 mg IV) may enroll after 5 subjects in Cohort 4 (300 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Cohort 7 (600 mg IV) may enroll after 5 subjects in Cohort 5 (600 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by

the Medical Monitor. Similarly, once the SC dose in Cohort 3 (150 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 8 (150 mg SC) can begin enrolling subjects on stable statin therapy. Likewise, once the SC dose in Cohort 4 (300 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 9 (300 mg SC) can begin enrolling subjects on stable statin therapy.

There will be no intra-subject dose escalation; subjects who are discontinued from the study (except those discontinued for adverse events) may be replaced. Subjects who withdraw early from the study must complete the study discharge evaluations, if possible.

### Dose-Limiting Toxicity

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

- Alanine transaminase (ALT) and/or aspartate transaminase (AST)  $>5 \times$  upper limit of normal (ULN) (confirmed by immediate repeat);
- ALT and/or AST  $>3 \times$  ULN AND total bilirubin  $>2.0 \times$  ULN (adjusted accordingly for subjects with Gilbert's whose total bilirubin is  $>2 \times$  ULN at baseline). Results will be confirmed by immediate repeat;
- ALT or AST  $>3 \times$  ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic injury, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia; or
- QTcF  $>500$  msec (confirmed on immediate repeat ECG).

Dosing within a cohort will be stopped and further dosing and/or dose escalation will be halted until unblinded safety information can be reviewed in the event that:

- $\geq 2$  subjects within the same dose cohort have the same serious adverse event;
- $\geq 2$  subjects within the same dose cohort have AST and/or ALT  $>5 \times$  ULN (confirmed by repeat);
- 1 subject within a dose cohort has AST and/or ALT  $>3 \times$  ULN AND total bilirubin  $>2.0 \times$  ULN (confirmed by repeat);
- 1 subject within a dose cohort has ALT or AST  $>3 \times$  ULN (confirmed by repeat) with the appearance or worsening of symptoms felt by the Investigator to be potentially related to hepatic injury, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia; or
- $\geq 2$  subjects within a dose cohort have QTcF  $>500$  msec (confirmed by repeat ECG).

## 4 SELECTION AND WITHDRAWAL OF SUBJECTS

### 4.1 Inclusion Criteria

For all cohorts, subjects must meet all the following criteria to be eligible to participate in the study:

1. Provision of written and signed informed consent (by subject) prior to any study-specific procedure;
2. Male or female,  $\geq 18$  and  $\leq 70$  years of age, inclusive, at screening;
3. Body mass index (BMI)  $\geq 18$  and  $\leq 38$  kg/m<sup>2</sup>;
4. Mild hypertensives on a stable dose of no more than one antihypertensive drug for subjects in the diet only cohorts and two antihypertensive agents in the statin cohorts are allowed to participate if they meet criteria listed above and below.
5. Female subjects must be of non-childbearing potential (ie, post-menopausal for  $\geq 1$  year [if in question, a follicle-stimulating hormone [FSH] of  $>40$  mIU/mL must be documented] or documented to have had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation);
6. Female subjects must not be pregnant or lactating/breast-feeding; As a precautionary measure all women will have a serum pregnancy test performed at screening.
7. Male subjects will either be surgically sterile or agree to use, from the time of Check-in (Study Day -1) until 90 days following the last dose of study drug, 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
8. Male subjects must refrain from sperm donation from the time of Check-in (Study Day -1) until 90 days following the last dose of study drug.

For Cohorts 1 to 7, subjects must also meet the following criteria to be eligible to participate in the study:

9. Subject has LDL-C  $\geq 100$  mg/dL and  $\leq 190$  mg/dL and TG  $\leq 250$  mg/dL at enrollment (screening visit) and has not received any lipid-lowering therapies within 30 days prior to screening (1 repeat test is allowed for subjects with LDL-C 90 mg/dL to 99 mg/dL, 190 mg/dL to 199 mg/dL or TG 251 mg/dL to 300 mg/dL); and
10. Subject is considered by the Investigator to be otherwise healthy, based on medical and surgical history review, a defined complete physical examination, as well as vital sign measurements, ECGs, and laboratory test results.

For Cohorts 8 and 9, subjects must meet the following criterion to be eligible to participate in the study:

11. Subject has LDL-C  $\geq 100$  mg/dL and TG  $\leq 250$  mg/dL at enrollment (screening visit) and is on stable dose of statin for  $\geq 4$  weeks (1 repeat test is allowed for subjects with LDL-C 90 mg/dL to 99 mg/dL or TG 251 mg/dL to 300 mg/dL).

## 4.2 Exclusion Criteria

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

1. History of any prior or concomitant clinical condition or acute and/or unstable systemic disease compromising subject inclusion, at the discretion of the Investigator, including but not limited to, the following: a history or presence of clinically significant cardiovascular, pulmonary, hepatic, gallbladder or biliary tract, hematologic, gastrointestinal, endocrine including diabetes, immunologic, dermatologic, neurologic, or psychiatric disease, which in the Investigator's opinion would not be suitable for the study from a subject safety consideration or could interfere with the results of the study;
2. Abnormal urinalysis (proteinuria greater than trace or any male or non-menstruating female with greater than trace hematuria) confirmed on repeat sample;
3. Uncontrolled cardiac arrhythmia or prolonged QT at screening (QTcF >450 msec for men and >470 msec for women) or known family history of prolonged QT or unexplained sudden cardiac death;
4. Blood pressure outside of the following ranges at screening: systolic blood pressure <90 mmHg or >160 mmHg or diastolic blood pressure <50 or >100 mmHg; 1 repeat measurement may be conducted per the Investigator's discretion; subjects on a stable dose of no more than one antihypertensive drugs in the non-statin cohorts and two antihypertensive agents in the statin cohorts are allowed to participate if they meet blood pressure criteria listed.
5. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen, or hepatitis C virus antibody;
6. Positive serum pregnancy test at screening (females only).
7. Laboratory Tests: Abnormal liver function test at Screening (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >2 × the upper limit of normal [ULN], total bilirubin >1.5 × ULN (subjects with mild unconjugated hyperbilirubinemia due to Gilbert's syndrome are not excluded), or alkaline phosphatase >2 × ULN based on appropriate age and gender normal values); TSH >1.5 x ULN with free T4 (FT4) within normal limits, CK >3 x ULN unless exercise related.
8. Moderate to severe renal insufficiency defined as an estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> at screening, as determined by the CKD-EPI Equation;
9. Is unable or refuses to abstain from smoking during confinement at the clinical research unit;
10. Has a history of prescription drug abuse, illicit drug use (including marijuana/tetrahydrocannabinol), or alcohol abuse according to medical history within 6 months prior to screening or any alcohol use for at least 48 hours prior to Check-in (Study Day -1); Subjects who test positive for alcohol at screening, but have no history of alcohol abuse, must be negative on retest at ~48 hours prior to check in for Study Day -1 and again at Day -1.
11. Use of, or treatment with, any prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications (except acetaminophen, which is allowed, and statins for Cohorts 8 and 9) within 14 days prior to Check-in (Study Day -1) and throughout the duration of the study (see Sections 5.6.1 and 5.6.2);

12. Has donated or lost a significant volume (>500 mL) of blood or plasma within 30 days prior to Check-in (Study Day -1);
13. Has had a blood transfusion within 4 weeks of randomization;
14. Was previously treated with LIB003 or any adnectin product;
15. Has a history of allergy to protein-based biologics including, but not limited to, mAbs and vaccines;
16. Has a history of any significant drug allergy (such as anaphylaxis or hepatotoxicity or immune mediated thrombocytopenia or anemia);
17. Has participated in another clinical study of an investigational agent or device concurrently or within 1 month prior to Screening, or use of an investigational agent within 30 days or 5 half-lives (if known), whichever is longer, prior to screening;
18. Has any other finding which, in the opinion of the Investigator, would compromise the subject's safety or participation in the study; or
19. Is an employee or family member of the Investigator or study site personnel.

### **4.3 Withdrawal Criteria**

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

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

If a subject discontinues prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the study discharge evaluations on Day 43. The reason for subject withdrawal must be documented in the electronic case report form (eCRF).

Withdrawn subjects may be replaced.

## 5 STUDY TREATMENTS

### 5.1 Treatment Groups

Following determination of eligibility, approximately 63 subjects will participate in this clinical study, including approximately 45 subjects to receive LIB003 and 18 subjects to receive placebo on Day 1. This study will consist of 9 separate and sequential dose cohorts. Within each cohort, 7 subjects will be randomized in a 5:2 ratio to receive a single dose of LIB003 (n=5) or placebo (n=2). The population in Cohorts 1 to 7 will include subjects with LDL-C levels  $\geq 100$  mg/dL and  $\leq 190$  mg/dL and TG levels  $\leq 250$  mg/dL who are not on a lipid-lowering therapy; Cohorts 8 and 9 will include subjects with LDL-C levels  $\geq 100$  mg/dL and TG levels  $\leq 250$  mg/dL who are on stable statin therapy. Dosing with LIB003 is planned for the first 7 cohorts as follows:

- Cohort 1: single dose of 25 mg SC,
- Cohort 2: single dose of 75 mg SC,
- Cohort 3: single dose of 150 mg SC,
- Cohort 4: single dose of 300 mg SC,
- Cohort 5: single dose of 600 mg SC,
- Cohort 6: single 300 mg IV infusion, and
- Cohort 7: single 600 mg IV infusion.

Provided that the 150 mg and 300 mg SC doses are safe and tolerable as outlined previously, they will be explored in subjects on stable statin therapy in Cohorts 8 and 9 as follows:

- Cohort 8: single dose 150 mg SC, and
- Cohort 9: single dose 300 mg SC.

### 5.2 Rationale for Dosing

LIB Therapeutics is developing LIB003 with the goal of achieving maximal and stable LDL-C lowering with a  $\geq 4$ -week dosing interval. The first in human starting dose of 25 mg is anticipated to be safe based on the lack of findings at the high LIB003 exposure levels achieved in the non-human primate GLP toxicology study. This dose is projected to yield a median LDL-C reduction of approximately 30% to 40%, roughly a half-maximal effect, for about 7 days; these PD effects have been shown to be safe and tolerable in the clinic with other PCSK9 inhibitors, including a closely related Adnectin analog of LIB003.

### 5.3 Randomization and Blinding

This study follows a randomized, double-blind, placebo-controlled design. Within each dosing cohort, 7 subjects will be randomized in a 5:2 ratio to receive a single dose of LIB003 (n=5) or placebo (n=2) on Day 1 according to a computer-generated randomization scheme. Because the color of the study drug product and placebo will not be identical, all therapy will be prepared by an unblinded pharmacist and administered by unblinded nurses who will be instructed not to discuss randomized treatment assignments. Additionally, for the IV cohorts, due to visual differences between LIB003 and saline (placebo), infusion bags containing study drug or placebo

will be covered to prevent product identification. Neither the pharmacist nor nurse(s) administering the study drug will be involved in any other aspects of the study or subject contact.

All SC cohorts and IV cohorts will each first enroll a sentinel group of 3 subjects, of which 2 subjects will receive LIB003 and 1 subjects will receive placebo in a double-blind fashion. The remaining 4 subjects will only be dosed after the available Day 4 (72 hours post-dose) safety data (adverse events and results from physical examinations, clinical laboratory tests, vital signs, and ECGs) from the sentinel subjects are assessed and deemed safe and tolerable by the Medical Monitor. Dose escalation will be based on the Medical Monitor's assessment of safety and tolerability data (adverse events, physical examination findings, clinical laboratory results, vital signs, and ECGs) through Day 8 for at least 5 subjects who received study drug. Cohort 6 (300 mg IV) may enroll after 5 subjects in Cohort 4 (300 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Cohort 7 (600 mg IV) may enroll after 5 subjects in Cohort 5 (600 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Similarly, once the SC dose in Cohort 3 (150 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 8 (150 mg SC) can begin enrolling subjects on stable statin therapy. Likewise, once the SC dose in Cohort 4 (300 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 9 (300 mg SC) can begin enrolling subjects on stable statin therapy.

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

#### **5.4 Breaking the Blind**

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

Because data emerging from each cohort of this exploratory study might be needed for timely decisions about adjustments to procedures in subsequent cohorts, including early termination of the study, data from completed cohorts at selected time points can be unblinded after documented completion and review of the corresponding eCRFs, prior to the formal locking of the study database. Also, designated staff of Medpace or LIB Therapeutics can be unblinded at any time. A single pharmacokineticist at Medpace as well as a single biostatistician, a single programmer in Medpace biostatistics and a single Medpace Medical Monitor may be unblinded in order to prepare preliminary summaries of PK, PD, and safety data as needed before data is more generally unblinded. These summaries will not reveal individual subjects' treatment assignments. Except as noted above, other members of LIB Therapeutics will remain blinded.

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

## 5.5 Drug Supplies

### 5.5.1 Formulation and Packaging

The drug product is a 250 mg/mL solution packaged in 0.7 mL volumes in 2 mL clear glass vials with stoppers and aluminum crimp seals.

The LIB003 formulation contains 20 mM histidine, 150 mM sodium chloride, 0.02% Polysorbate 80 at pH 6.8.

### 5.5.2 Study Drug Preparation and Dispensing

Trained medical personnel will administer LIB003 or placebo to subjects within the clinical facility. Site personnel should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by LIB Therapeutics as outlined in the pharmacy manual. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact LIB Therapeutics immediately.

Instructions for LIB003 preparation are documented in a separate manual.

### 5.5.3 Study Drug Administration

Study drug or matching placebo will be administered on Day 1 as a single ascending dose in sequential dosing cohorts. Study drug will be administered under the supervision of the unblinded site personnel who will not be involved in further subject assessments.

In Cohorts 6 and 7, LIB003 300 mg and 600 mg, respectively, or matching placebo will be administered as an IV infusion in normal saline over 20 minutes; due to visual differences between LIB003 and saline (placebo), infusion bags containing study drug or placebo will be covered to prevent product identification. In all other cohorts, LIB003 (25 mg, 75 mg, 150 mg, 300 mg, and 600 mg) or matching placebo will be administered as a SC injection.

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

### Dose Escalation

All cohorts will each first enroll a sentinel group of 3 subjects, of which 2 will receive LIB003 and 1 will receive placebo in a double-blind fashion. The remaining 4 subjects will only be dosed after the available Day 4 (72 hours post dose) safety data from the sentinel subjects are assessed and deemed safe and tolerable by the Medical Monitor.

Dose escalation will be based on the Medical Monitor's assessment of safety and tolerability data (adverse events, physical examination findings, clinical laboratory results, vital signs, and electrocardiograms [ECGs]) through Day 8 for at least 5 subjects who received study drug. Cohort 6 (300 mg IV) may enroll after 5 subjects in Cohort 4 (300 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Cohort 7 (600 mg IV) may enroll after 5 subjects in Cohort 5 (600 mg SC) have completed Day 8 and the dose has been deemed safe and tolerable by the Medical Monitor. Similarly, once the SC dose in Cohort 3 (150 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 8 (150 mg SC) can begin enrolling subjects on stable statin therapy. Likewise, once the SC dose in Cohort 4 (300 mg SC) is determined safe and tolerable in at least 5 subjects after 8 days, Cohort 9 (300 mg SC) can begin enrolling subjects on stable statin therapy.

Dose escalation decisions will be documented in the appropriate file before the next cohort of subjects is dosed. There will be no intra-subject dose escalation.

For stopping rules and dose-limiting toxicities, see Section 3.2.

#### 5.5.4 Treatment Compliance

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

#### 5.5.5 Storage and Accountability (see separate Pharmacy Manual)

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

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

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

### 5.6 Prior and Concomitant Medications and/or Procedures

#### 5.6.1 Excluded Medications and/or Procedures

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

Medications include prescription drugs, 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, no concomitant medication will be permitted unless the rationale for use is discussed between the Investigator and the Sponsor, and is clearly documented. The following medications are exceptions:

- Statins are allowed for Cohorts 8 and 9;
- One antihypertensive drug for subjects in the non-statin cohorts and two antihypertensive agents in the statin cohorts
- Medications used to treat adverse events may only be prescribed after consultation with the Medical Monitor (with the exception of acetaminophen), unless there is an immediate medical need to ensure the well-being of the subject that should not be delayed. All therapy and/or medication administered to manage adverse events should be recorded in the appropriate eCRF;

- Acetaminophen is allowed at a maximum dose of 2 g per day up to 96 hours prior to study drug dosing. During the confinement period at the clinical research unit, subjects will be restricted from the use of acetaminophen and other non-prescription medications beginning 4 hours prior to study drug administration through 4 hours after study drug dosing, unless deemed necessary to treat an adverse event by the Investigator; and
- Hormone replacement therapy use is only permitted if initiated at least 2 months prior to the first dose of study drug.

#### 5.6.2 Excluded Medications and/or Procedures

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

- Any other investigational drug taken within 30 days or 5 half-lives (whichever is longer) prior to screening; and
- Use of, or treatment with, any prescription drugs (other than statins and antihypertensive agents as specified above), herbal products, vitamins, minerals, and OTC medications within 14 days prior to Check-in (Study Day -1) and throughout the duration of the study. Exceptions may be made on a case-by-case basis following discussion and agreement between the Investigator and the Sponsor.

#### 5.6.3 Restrictions and Dietary Guidelines

Subjects must not participate in strenuous physical activity or exercise from 48 hours prior to Day 1 and throughout the duration of the study.

Subjects are restricted from using alcohol for the duration of confinement at the clinical research unit.

There are fasting requirements around dosing on specific days. Fasting is defined as no food or caloric beverages for at least 10 hours. Subjects will be permitted to have 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, both prescribed and OTC, in the eCRF and the source document. This includes drugs used on a chronic and as-needed basis. Subjects should be discouraged from starting any new medication, both prescribed and OTC, without consulting the Investigator, unless the new medication is required for an emergency.

## 6 STUDY PROCEDURES

### 6.1 Informed Consent

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

### 6.2 Study Schedule for the Subcutaneous Dosing Cohort

When multiple study procedures are scheduled at the same time point, the order of procedures should be as follows: perform ECG, obtain vital signs, and collect blood sample. A  $\pm 2$ -day window is allowed for all post-confinement clinic visits, which include Days 8, 11, 15, 18, 22, 29, 36, and 43 (and continued weekly visits for subjects whose LDL-C levels are not within 20% of baseline; or 4 week visits for subjects with positive anti-drug antibodies at Day 43) for the SC cohorts. The baseline LDL-C for determining continued weekly visits if LDL-C is  $>20\%$  below baseline at Day 43 will be the lowest of the pre-dosed Friedewald calculated LDL-C (i.e. screening, Day -1 or Day 1). As Friedewald underestimates LDL-C  $<70$  mg/dL, post dose LDL-C will be by ultracentrifugation if LDL-C by Friedewald is  $>20\%$  from baseline. A  $\pm 15$ -minute window for all post-dose procedures and blood draws and a  $\pm 30$ -minute window for ECGs and physical examinations are allowed.

All blood samples, with the exception of those collected 8, 12 and 36 hours post-dose, should be collected while the subject is in a fasted state ( $\geq 10$  hours).

#### 6.2.1 Screening Period (Up to Day -28)

Screening procedures must be performed within the 28 days prior to dosing. The following procedures will be performed at the screening visit for the SC cohorts:

- Obtain informed consent,
- Evaluate inclusion/exclusion criteria,
- Obtain demographics and medical history,
- Record prior and concomitant medications,
- Perform physical examination,
- Measure height and weight and calculate BMI,
- Perform 12-lead ECG,
- Record vital signs,
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:

- Serology,
- Safety chemistry and hematology,
- Lipid panel, and
- Serum pregnancy test (all women).

#### 6.2.2 Study Day -1

If the screening visit occurs on Day -1, the procedures for screening and Day -1 will be combined. Subjects designated as 'reserve' and admitted on Day -1 but not required, or randomized, on Day 1 must undergo repeat Day -1 assessments to continue in the study, if >28 days since screen visit a combined screen/Day -1 visit will be carried out. The following procedures will be performed on Day -1 for the SC cohorts:

- Begin confinement;
- Evaluate inclusion/exclusion criteria;
- Obtain medical history;
- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel, and
- Assess adverse events.

#### 6.2.3 Study Day 1

The following procedures will be performed on Day 1 for the SC cohorts:

- Continue confinement;
- Record prior and concomitant medications;
- Perform physical examination (pre-dose) (if the screening physical examination was performed within 24 hours of study drug administration, it does not need to be repeated on Day 1);
- Perform 12-lead ECG;

- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature) (pre-dose and at 2, 4, and 8 hours post-dose);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology;
  - Lipid panel (pre-dose and at 4 and 12 hours post-dose);
  - PK (pre-dose and at 2, 4, 8, and 12 hours post-dose);
  - PCSK9 (total and free) (pre-dose and at 2, 4, 8 and 12 hours post-dose);
  - Immunogenicity (pre-dose); and
  - Exploratory biomarkers (pre-dose);
- Randomize eligible subjects;
- Administer SC dose of study drug;
- Assess injection site (pre-dose and 12 hours post-dose); and
- Assess adverse events.

#### 6.2.4 Study Day 2

The following procedures will be performed on Day 2 for the SC cohorts:

- Continue confinement;
- Record prior and concomitant medications;
- Perform 12-lead ECG (24 hours post-dose);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel (24 and 36 hours post-dose),
  - PK (24 and 36 hours post-dose), and
  - PCSK9 (total and free) (24 and 36 hours post-dose),
- Assess injection site; and
- Assess adverse events.

#### 6.2.5 Study Day 3

The following procedures will be performed on Day 3 for the SC cohorts:

- Continue confinement;

- Record prior and concomitant medications;
- Perform 12-lead ECG (48 hours post-dose);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel (48 hours post-dose),
  - PK (48 hours post-dose),
  - PCSK9 (total and free) (48 hours post-dose), and
  - Exploratory biomarkers (48 hours post-dose),
- Assess injection site; and
- Assess adverse events.

#### 6.2.6 Study Day 4

The following procedures will be performed on Day 4 for the SC cohorts:

- Record prior and concomitant medications;
- Perform physical examination (72 hours post-dose);
- Obtain body weight;
- Perform 12-lead ECG (72 hours post-dose);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - PCSK9 (total and free) (72 hours post-dose), and
  - PK (72 hours post-dose),
- Assess injection site;
- Assess adverse events; and
- Discharge subject from the unit on the morning of Day 4.

#### 6.2.7 Study Day 8

The following procedures will be performed on Day 8 for the SC cohorts:

- Record prior and concomitant medications;
- Perform physical examination;

- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK, and
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.2.8 Study Day 11

The following procedures will be performed on Day 11 for the SC cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - PK, and
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.2.9 Study Day 15

The following procedures will be performed on Day 15 for the SC cohorts:

- Record prior and concomitant medications;
- Obtain body weight;
- Perform 12-lead ECG;

- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity, and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.2.10 Study Day 18

The following procedures will be performed on Day 18 for the SC cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK, and
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.2.11 Study Day 22

The following procedures will be performed on Day 22 for the SC cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);

- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free), and
  - Immunogenicity,
- Assess injection site; and
- Assess adverse events.

#### 6.2.12 Study Day 29

The following procedures will be performed on Day 29 for the SC cohorts:

- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis,
  - Urine drug and alcohol screen, and
  - Urine pregnancy test,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity, and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.2.13 Study Day 36

The following procedures will be performed on Day 36 for the SC cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity, and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.2.14 Study Day 43 (Study Discharge)

The following procedures will be performed on Day 43 for the SC cohorts:

- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen, and
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity (Note: subjects with positive antibody results at Day 43 will return for a follow-up assessment approximately every 28 days for antibody and immunological

adverse event assessment until resolved or until judged to be chronic or stable by the Investigator), and

- Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.2.15 Weekly Follow-Up Period

The end of treatment for subjects completing the study is Day 43. The following follow-up procedures will be performed at weekly intervals (Days 50, 57, 64 etc.) for subjects in the SC cohorts whose LDL-C levels have not returned to within 20% of baseline:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.2.16 Early Termination Visit

The end of treatment for subjects completing the study is Day 43. For subjects who are withdrawn from the study prior to completion, all Day 43 procedures will be performed at an early termination visit. These procedures include the following:

- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen, and

- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity (Note: subjects with positive antibody results at Day 43 will return for a follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator), and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

### **6.3 Study Schedule for the Intravenous Dosing Cohort**

When multiple study procedures are scheduled at the same time point, the order of procedures should be as follows: perform ECG, obtain vital signs, and collect blood sample. A  $\pm 2$ -day window is allowed for all post-confinement clinic visits, which include Days 5, 8, 11, 15, 18, 22, 29, and 43 (and continued weekly visits for subjects whose LDL-C levels are not within 20% of baseline; or 4 week visits for subjects with positive anti-drug antibodies at Day 43) for the IV cohorts. The baseline LDL-C for determining continued weekly visits if LDL-C is  $>20\%$  lower than baseline at Day 43 will be the lowest of the pre-dosed Friedewald calculated LDL-C (i.e. screening, Day -1 or Day 1). As Friedewald underestimates LDL-C  $<70$  mg/dL, post dose LDL-C will be by ultracentrifugation if LDL-C by Friedewald is  $>20\%$  lower than baseline. A  $\pm 15$  minute window for all post-dose procedures and blood draws and a  $\pm 30$  minute window for ECGs and physical examinations are allowed.

All blood samples, with the exception of those collected 12 and 36 hours post-dose, should be collected while the subject is in a fasted state ( $\geq 10$  hours) with water allowed.

#### **6.3.1 Screening Period (Up to Day -28)**

Screening procedures must be performed within the 28 days prior to dosing. The following procedures will be performed at the screening visit for the IV cohorts:

- Obtain informed consent;
- Evaluate inclusion/exclusion criteria;
- Obtain demographics and medical history;
- Record prior and concomitant medications;
- Perform physical examination;
- Measure height and weight and calculate BMI;
- Perform 12-lead ECG;

- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Serology,
  - Safety chemistry and hematology,
  - Lipid panel, and
  - Serum pregnancy test (all women).

### 6.3.2 Study Day -1

If the screening visit occurs on Day -1, the procedures for screening and Day -1 will be combined. Subjects designated as 'reserve' and admitted on Day -1 but not required, or randomized, on Day 1 must undergo repeat Day -1 assessments to continue in the study, if >28 days since screen visit a combined screen/Day -1 visit will be carried out. The following procedures will be performed on Day -1 for the IV cohorts:

- Begin confinement;
- Evaluate inclusion/exclusion criteria;
- Obtain medical history;
- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology, and
  - Lipid panel
- Assess adverse events.

### 6.3.3 Study Day 1

The following procedures will be performed on Day 1 for the IV cohorts:

- Continue confinement;
- Record prior and concomitant medications;
- Perform physical examination (pre-dose) (if the screening physical examination was performed within 24 hours of study drug administration, it does not need to be repeated on Day 1);
- Perform 12-lead ECG (pre-dose, at 10 minutes after termination of infusion, and at 1, 2, 4, and 8 hours after termination of infusion);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature) (pre-dose, at 10 minutes (mid-infusion) and at termination of infusion, and at 2, 4, and 8 hours after termination of infusion);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology;
  - Lipid panel (pre-dose and at 4, and 12 hours after termination of infusion);
  - PK (pre-dose, at termination of infusion, and at 1, 2, 4, 8, and 12 hours after termination of infusion);
  - PCSK9 (total and free) (pre-dose and at 1, 2, 4, 8 and 12 hours after termination of infusion);
  - Immunogenicity (pre-dose); and
  - Exploratory biomarkers (pre-dose);
- Randomize eligible subjects;
- Administer IV infusion;
- Assess injection site (pre-dose and 12 hours after termination of infusion); and
- Assess adverse events.

#### 6.3.4 Study Day 2

The following procedures will be performed on Day 2 for the IV cohorts:

- Continue confinement;
- Record prior and concomitant medications;
- Perform 12-lead ECG (24 hours from start of infusion);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel (24 and 36 hours from start of infusion),

- PK (24 and 36 hours from start of infusion), and
- PCSK9 (total and free) (24 and 36 hours from start of infusion),
- Assess injection site; and
- Assess adverse events.

#### 6.3.5 Study Day 3

The following procedures will be performed on Day 3 for the IV cohorts:

- Continue confinement;
- Record prior and concomitant medications;
- Perform 12-lead ECG (at least 48 hours from start of infusion);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel (48 hours from start of infusion),
  - PK (48 hours from start of infusion),
  - PCSK9 (total and free) (48 hours from start of infusion), and
  - Exploratory biomarkers (48 hours from start of infusion),
- Assess injection site; and
- Assess adverse events.

#### 6.3.6 Study Day 4

The following procedures will be performed on Day 4 for the IV cohorts:

- Record prior and concomitant medications;
- Perform physical examination (at least 72 hours from start of infusion);
- Obtain body weight;
- Perform 12-lead ECG (at least 72 hours from start of infusion);
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for urinalysis;
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - PK (72 hours from start of infusion), and
  - PCSK9 (total and free) (72 hours from start of infusion),

- Assess injection site;
- Assess adverse events; and
- Discharge subject from the unit on the morning of Day 4.

#### 6.3.7 Study Day 5

The following procedures will be performed on Day 5 for the IV cohorts:

- Record prior and concomitant medications;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK, and
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.3.8 Study Day 8

The following procedures will be performed on Day 8 for the IV cohorts:

- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,

- PK, and
- PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.3.9 Study Day 11

The following procedures will be performed on Day 11 for the IV cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - PK, and
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.3.10 Study Day 15

The following procedures will be performed on Day 15 for the IV cohorts:

- Record prior and concomitant medications;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),

- Immunogenicity, and
- Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.3.11 Study Day 18

The following procedures will be performed on Day 18 for the IV cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK, and
  - PCSK9 (total and free),
- Assess injection site; and
- Assess adverse events.

#### 6.3.12 Study Day 22

The following procedures will be performed on Day 22 for the IV cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free), and
  - Immunogenicity,

- Assess injection site; and
- Assess adverse events.

#### 6.3.13 Study Day 29

The following procedures will be performed on Day 29 for the IV cohorts:

- Record prior and concomitant medications;
- Perform physical examination;
- Obtain body weight;
- Perform 12-lead ECG;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis,
  - Urine drug and alcohol screen, and
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity, and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.3.14 Study Day 36

The following procedures will be performed on Day 36 for the IV cohorts:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis, and
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,

- PK,
- PCSK9 (total and free),
- Immunogenicity, and
- Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.3.15 Study Day 43 (Study Discharge)

The following procedures will be performed on Day 43 for the IV cohorts:

- Record prior and concomitant medications;
- Perform physical examination and obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis,
  - Urine drug and alcohol screen, and
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity (Note: subjects with positive antibody results at Day 43 will return for a follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator), and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.3.16 Weekly Follow-Up Period

The end of treatment for subjects completing the study is Day 43. The following follow-up procedures will be performed at weekly intervals (Days 50, 57, 64 etc.) for subjects in the IV cohorts whose LDL-C levels have not returned to within 20% of baseline:

- Record prior and concomitant medications;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:

- Urinalysis, and
- Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free)
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

#### 6.3.17 Early Termination Visit

The end of treatment for subjects completing the study is Day 43. For subjects who are withdrawn from the study prior to completion, all Day 43 procedures will be performed at an early termination visit. These procedures include the following:

- Record prior and concomitant medications;
- Perform physical examination and obtain body weight;
- Record vital signs (blood pressure, heart rate, respiratory rate, and temperature);
- Collect urine sample for the following:
  - Urinalysis,
  - Urine drug and alcohol screen,
- Collect blood sample for the following:
  - Safety chemistry and hematology,
  - Lipid panel,
  - PK,
  - PCSK9 (total and free),
  - Immunogenicity (Note: subjects with positive antibody results at Day 43 will return for a follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator), and
  - Exploratory biomarkers,
- Assess injection site; and
- Assess adverse events.

## 7 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

All blood samples, with the exception of those collected 12 and 36 hours post-dose, should be collected while the subject is in a fasted state ( $\geq 10$  hours). 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 a laboratory manual.

### 7.1 Pharmacokinetic Parameters

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

Pharmacokinetic parameters for SC dosing will include the following:

- $C_{\max}$  – maximum observed plasma concentration,
- $T_{\max}$  – time of maximum observed plasma concentration,
- $AUC_{0-t}$  – area under the plasma concentration-time curve from time 0 to the time of last quantifiable plasma concentration,
- $AUC_{\text{inf}}$  – area under the plasma concentration-time curve from time 0 extrapolated to infinite time,
- T-HALF – plasma elimination half-life,
- CL/F – apparent total body clearance,
- Vz/F – apparent volume of distribution, and
- F – absolute bioavailability of total LIB003.

Pharmacokinetic parameters for SC dosing will be measured at the time points specified in Table 1 and Table 2. Additional PK parameters may be calculated if deemed appropriate. If subjects develop ADAs that impact exposure, data will be reported both with and without the ADA-affected exposure data.

Pharmacokinetic parameters for IV dosing will include the following:

- $C_{\max}$  – maximum observed plasma concentration,
- $T_{\max}$  – time of maximum observed plasma concentration,
- $AUC_{0-t}$  – area under the plasma concentration-time curve from time 0 to the time of last quantifiable plasma concentration,
- $AUC_{\text{inf}}$  – area under the plasma concentration-time curve from time 0 extrapolated to infinite time,
- T-HALF – plasma elimination half-life,
- CL – total body clearance, and
- Vz – volume of distribution.

Absolute bioavailability of LIB003 following SC administration will be assessed for the 300 mg and 600 mg doses since these are the doses common to both routes of administration.

Pharmacokinetic parameters for IV dosing will be measured at the time points specified in Table 3 and Table 4. Additional PK parameters may be calculated if deemed appropriate. If subjects develop ADAs that impact exposure, data will be reported both with and without the ADA-affected exposure data.

## **7.2 Pharmacodynamic Endpoints**

The secondary objectives to assess the PD effects of single SC and IV doses of LIB003 will be measured by the following secondary endpoints:

- Plasma unbound (free) PCSK9 concentrations and serum LDL-C;
- Serum lipids, including TC, HDL-C, VLDL-C, and TG;
- Apo B, apo A1, and Lp(a) serum concentrations; and
- Total plasma PCSK9 concentrations.

### **7.2.1 Immunogenicity Endpoints**

Another secondary objective is to assess the occurrence and frequency of ADAs following single SC and IV doses of LIB003. Anti-LIB003 antibodies will be measured at the time points specified in Table 1 and Table 2 for the SC cohorts and Table 3 and Table 4 for the IV cohorts. As results of ADA analysis will not be performed until Day 15 post-dose, they will not form part of the safety analysis at Day 3 or Day 8 for continued dosing of a cohort or to proceed to the next cohort, respectively.

### **7.2.2 Exploratory Endpoints**

Exploratory objectives include an assessment of the effects of single SC and IV doses of LIB003 on other lipid and cardiovascular risk biomarkers, including but not limited to hs-CRP, as appropriate. Serum hs-CRP and potentially other parameters may be assessed from saved, stored, frozen serum aliquots obtained at the time points specified in Table 1 and Table 2 for the SC cohorts and Table 3 and Table 4 for the IV cohorts.

The exploratory objective to compare the PD effects of LIB003 in healthy subjects not on statin therapy and healthy subjects who are on stable statin therapy will be measured using the endpoints in Section 7.2.

Additionally, an extra exploratory biomarker serum aliquot will be collected and stored frozen for potential assessment of additional lipid or other biomarkers related to cardiovascular disease.

## **8 SAFETY ASSESSMENTS**

### **8.1 Adverse Events**

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

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

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

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

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

#### **8.1.1 Adverse (Drug) Reaction**

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

#### **8.1.2 Unexpected Adverse Drug Reaction**

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

### 8.1.3 Assessment of Adverse Events by the Investigator

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

#### Assessment of Severity:

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

#### Causality Assessment:

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

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

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

The following factors should also be considered:

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

## 8.2 Serious Adverse Events

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

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

## 8.3 Serious Adverse Event Reporting – Procedures for Investigators

### Initial Reports

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

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

Safety Contact Information: Medpace Clinical Safety

Medpace SAE reporting line – USA:

Telephone: +1-800-730-5779, dial 3 or 513-579-9911, dial 3

Fax: +1-866-336-5320 or 513-579-0444

e-mail: medpace-safetynotification@medpace.com

#### Follow-Up Reports

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

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

#### **8.4 Pregnancy Reporting**

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

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

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

#### **8.5 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 FDA and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

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

The Sponsor will also inform all Investigators as required.

#### **8.6 Clinical Laboratory Evaluations**

Results of clinical laboratory tests performed on Day -1 must be available prior to dosing. Clinical laboratory profiles for hematology, serum chemistry, and urinalysis will be evaluated from

samples collected after  $\geq 10$  hours of fasting at the time points specified in Table 1 and Table 2 for the SC cohorts and Table 3 and Table 4 for the IV cohorts.

For all women a serum pregnancy test will be performed at screening.

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

#### 8.6.1 Potential Drug-Induced Liver Injury

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

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

#### 8.7 Immunogenicity

Subjects with positive antibody results at Day 43 will return for follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator.

#### 8.8 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at all study visits at the time points specified in Table 1 and Table 2 for the SC cohorts and Table 3 and Table 4 for the IV cohorts. Blood pressure and heart rate will be measured after the subject has been seated or supine for  $\geq 5$  minutes.

#### 8.9 Electrocardiograms

Twelve-lead (single) ECGs will be assessed at all study visits at the time points ( $\pm 30$  minutes) specified in Table 1 and Table 2 for the SC cohorts and Table 3 and Table 4 for the IV cohorts. Subjects should be resting in the supine position for  $\geq 10$  minutes prior to each 12-lead ECG.

#### 8.10 Physical Examinations

Physical examinations will be performed throughout the study at the time points ( $\pm 30$  minutes) specified in Table 1 and Table 2 for the SC cohorts and Table 3 and Table 4 for the IV cohorts. Injection site reactions will be monitored by physical examination.

#### 8.11 Drug and Alcohol Screen

A urine screen for drugs of abuse (including amphetamine, barbiturates, benzodiazepines, cocaine, tetrahydrocannabinol, opiates, and phencyclidine) will be assessed at the time points specified in Table 1 for the SC cohorts and Table 3 for the IV cohorts. Alcohol testing may be performed by urine screen or breath test at the same time points.

## **9 STATISTICS**

### **9.1 Statistical Methods**

### **9.2 Analysis Populations**

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

The PD Population is defined as all subjects with any post-baseline PD measurement.

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

#### **9.2.1 Analysis of Efficacy**

Not applicable.

#### **9.2.2 Pharmacodynamic Analysis**

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

##### **9.2.2.1 Exploratory biomarker analysis**

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

##### **9.2.2.2 Immunogenicity analyses**

Immunogenicity data will be listed.

#### **9.2.3 Pharmacokinetic Analysis**

Pharmacokinetic analysis will be performed based on the PK Evaluable Population. Power Law model will be used to assess the dose proportionality for Cohorts 1 to 5 (SC doses). Bioavailability analysis of log-transformed PK parameters will be performed for Cohort 6 and 7 (IV doses) and corresponding SC dose cohorts with a 2-sample t-test. All PK parameters and PK concentrations will be summarized descriptively.

#### **9.2.4 Analysis of Safety**

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

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

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

#### 9.2.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

#### 9.2.6 Interim Analysis

No interim analysis is planned for this study.

### 9.3 Sample Size Determination

Although the number of subjects is not based on statistical power considerations, administration of LIB003 to 5 subjects in each cohort provides an 80% probability of observing at least 1 occurrence in that cohort of any adverse event which would occur with a 24% incidence in the population from which the sample is drawn. Approximately 63 subjects will participate in this clinical study, including 45 to receive LIB003 and 18 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 has been accounted for.

#### 10.1.2 Computer Systems

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

#### 10.1.3 Data Entry

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

#### 10.1.4 Medical Information Coding

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

#### 10.1.5 Data Validation

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

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

### **10.2 Record Keeping**

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

## **11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL**

### **11.1 Ethical Conduct of the Study**

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

### **11.2 Institutional Review Board**

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

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

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

### **11.3 Informed Consent**

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

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

### **11.4 Study Monitoring Requirements**

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

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

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

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

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

### **11.5 Disclosure of Data**

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

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

### **11.6 Retention of Records**

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

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

### **11.7 Publication Policy**

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

## **11.8 Financial Disclosure**

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

## **12 STUDY ADMINISTRATIVE INFORMATION**

### **12.1 Protocol Amendments**

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

### **12.2 Address List**

#### **12.2.1 Sponsor**

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

#### **12.2.2 Contract Research Organization**

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

#### **12.2.3 Drug Safety**

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

#### **12.2.4 Biological Specimens**

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

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## APPENDIX A: SCHEDULE OF PROCEDURES

**Table 1. Schedule of Procedures – Subcutaneous Dosing Cohorts**

Study Day Study Procedure	Up to -28 [1]	-1 [1]	1	2	3	4	8	11	15	18	22	29	36	43/ ET	Weekly FUP [2]
Informed consent	X														
Confinement		X	X	X	X	X [3]									
Inclusion/exclusion criteria	X	X													
Demographics	X														
Medical history [4]	X	X													
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X [5]	X [5]	X [5]			X	X					X		X	
Weight	X	X				X	X		X			X		X	
Height and BMI calculation	X														
Vital signs [6]	X	X	X [6]	X	X	X	X	X	X	X	X	X	X	X	X
Serology [7]	X														
Safety laboratory tests [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK blood sample [9]			X	X	X	X	X	X	X	X	X	X	X	X	X
TSH, FSH	X														
PCSK9 measurement [10]			X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel [11]	X	X	X	X	X		X		X	X	X	X	X	X	X
Immunogenicity assessment			X [12]						X		X	X	X	X [13]	
Exploratory biomarkers [14]			X		X				X			X	X	X	
12-lead ECG [15]	X	X	X	X	X	X	X		X			X			X
Pregnancy test [16]	X														
Urine drug and alcohol screen [17]	X	X					X	X	X	X	X	X	X	X	X
Randomization			X												
Study drug administration			X												
Injection site assessment			X [18]	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X

See footnotes on next page.

All blood samples, with the exception of those collected 8, 12 and 36 hours post-dose, should be collected while the subject is in a fasted state ( $\geq 10$  hours).

When multiple study procedures are scheduled at the same time point, the order of procedures should be as follows: perform ECG, obtain vital signs, and collect blood sample.

A  $\pm 2$ -day window is allowed for all post-confinement clinic visits.

A  $\pm 15$ -minute window for all post-dose procedures and blood draws and a  $\pm 30$ -minute window for ECGs and physical examinations are allowed.

1. If the screening visit occurs on Day -1, the procedures from these visits will be combined. Subjects designated as 'reserve' and admitted on Day -1 but not required, or randomized, on Day 1 must undergo repeat Day -1 assessments to continue in the study, if  $>28$  days since screen visit a combined screen/Day -1 visit will be carried out.
  2. Procedures will be performed at weekly intervals (Days 50, 57, 64 etc.) for subjects in the SC cohorts whose LDL-C levels have not returned to within 20% of baseline. The baseline LDL-C for determining continued weekly visits if LDL-C is  $>20\%$  from baseline at Day 43 will be the lowest of the pre-dosed Friedewald calculated LDL-C (i.e. screening, Day -1 or Day 1). As Friedewald underestimates LDL-C  $<70$  mg/dL, post dose LDL-C will be by ultracentrifugation if LDL-C by Friedewald is  $>20\%$  from baseline.
  3. Subjects will be confined for 72 hours post-dose; discharge from the unit is expected on the morning of Day 4.
  4. Medical history will include all toxicities and allergies to previous treatments.
  5. A physical examination is required in the 24 hours prior to study drug administration. If the screening visit and/or Day -1 physical examination was performed within 24 hours of study drug administration, it does not need to be repeated on Day 1.
  6. Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the subject has been seated or supine for  $\geq 5$  minutes. On Day 1, vital signs will be measured pre-dose and at 2, 4, and 8 hours post-dose.
  7. Serology will include HIV, HBsAg, and HCV screening.
  8. Safety laboratory tests will include chemistry, hematology, and urinalysis.
  9. During confinement, PK blood samples will be collected pre-dose and 2, 4, 8, 12, 24, 36, 48, and 72 hours post-dose.
  10. During confinement, blood samples for measurement of total and unbound (free) PCSK9 will be collected pre-dose and 2, 4, 8, 12, 24, 36, 48, and 72 hours post-dose.
  11. The lipid panel includes LDL-C (calc by Friedewald and Hopkins formulas), TC, HDL-C, VLDL-C (calculated by Friedewald and Hopkins), TG. During confinement, blood samples for lipid measurement will be collected pre dose and at 4, 12, 24, 36, and 48 hours post-dose. Only TC, HDL-C, and TG will be measured, and Friedewald and Hopkins formulas used to calculate LDL-C and VLDL-C at these time points, and the remaining serum will be frozen at  $-70^{\circ}\text{C}$  for apolipoprotein measurements if needed. LDL-C and VLDL-C (measured by preparative ultracentrifugation) and apo B, apo A1, and Lp(a) will be measured on Days 1 (pre-dose), 8, 15, 29 and 43.
  12. Blood samples for immunogenicity assessment will be collected pre-dose on Day 1.
  13. Subjects with positive antibody results at Day 43 will return for follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator.
  14. Exploratory biomarker blood samples will be collected and frozen for potential assessment of additional lipid or other biomarkers. During confinement, blood samples for exploratory biomarkers will be collected pre-dose and at 48 hours post-dose.
  15. During confinement, 12-lead (single) ECGs will be performed pre-dose and at 8, 24, 48, and 72 hours post-dose. Subjects should be resting in the supine position for  $\geq 10$  minutes prior to each 12-lead ECG.
  16. A serum pregnancy test will be performed at screening on all women
  17. Alcohol testing may be performed by urine screen or breath test at the same time points. Subjects who test positive for alcohol at screening, but have no history of alcohol abuse, must be negative on retest at least 48 hours prior to check in for Study Day -1 and again at Day -1.
  18. On Day 1, injection site assessments will be performed pre-dose and 12 hours post-dose.
- apo = apolipoprotein; BMI = body mass index; ECG = electrocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; ET = early termination; FUP = follow-up period; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; SC = subcutaneous; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

**Table 2. Timed Assessments During Confinement – Subcutaneous Dosing Cohorts**

Study Day	Day 1					Day 2		Day 3	Day 4
	0 hr (pre-dose)	2 hr	4 hr	8 hr	12 hr	24 hr	36 hr	48 hr	72 hr
Physical examination	X [1]								X
12-lead ECG [2]	X			X		X		X	X
Vital signs [3]	X	X	X	X		X		X	X
PK blood sample	X	X	X	X	X	X	X	X	X
PCSK9 measurement [4]	X	X	X	X	X	X	X	X	X
Lipid panel [5]	X		X		X	X	X	X	
Immunogenicity assessment	X								
Exploratory biomarkers [6]	X							X	
Study drug administration	X								
Injection site assessment	X				X	X		X	X

All blood samples, with the exception of those collected 8, 12 and 36 hours post-dose, should be collected while the subject is in a fasted state (≥10 hours).  
When multiple study procedures are scheduled at the same time point, the order of procedures should be as follows: perform ECG, obtain vital signs, and collect blood sample.  
Subjects with positive antibody results at Day 43 will return for follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator.  
Time points are relative to administration of study drug. A ±15-minute window for all post-dose procedures and blood draws and a ±30 minute window for ECGs and physical examinations are allowed.

1. A physical examination is required in the 24 hours prior to study drug administration. If the screening and/or Day -1 physical examination was performed within 24 hours of study drug administration, it does not need to be repeated on Day 1.
2. Subjects should be resting in the supine position for ≥10 minutes prior to each 12-lead (single) ECG.
3. Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the subject has been seated or supine for ≥5 minutes.
4. During confinement, blood samples for measurement of total and unbound (free) PCSK9 will be collected pre-dose and 2, 4, 8, 12, 24, 36, 48, and 72 hours post-dose
5. The lipid panel includes LDL-C (calc by Friedewald and Hopkins formulas), TC, HDL-C, VLDL-C (calculated by Friedewald and Hopkins), TG. During confinement, blood samples for lipid measurement will be collected pre dose and at 4, 12, 24, 36, and 48 hours post-dose. Only TC, HDL-C, and TG will be measured, and Friedewald and Hopkins formulas used to calculate LDL-C and VLDL-C at these time points, and the remaining serum will be frozen at -70°C for apolipoprotein measurements if needed. LDL-C and VLDL-C (measured by preparative ultracentrifugation) and apo B, apo A1, and Lp(a) will be measured on Days 1 (pre-dose), 8, 15, 29 and 43.
6. Exploratory biomarker blood samples will be collected and frozen for potential assessment of additional lipid or other biomarkers.

apo = apolipoprotein; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

**Table 3. Schedule of Procedures – Intravenous Dosing Cohorts**

Study Day	Up to -28 [1]	-1 [1]	1	2	3	4	5	8	11	15	18	22	29	36	43/ET	Weekly FUP [2]
Informed consent	X															
Confinement		X	X	X	X	X [3]										
Inclusion/exclusion criteria	X	X														
Demographics	X															
Medical history [4]	X	X														
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [5]	X	X	X			X		X					X		X	
Weight	X	X				X		X		X			X		X	
Height and BMI calculation	X															
Vital signs [6]	X	X	X [6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Serology [7]	X															
Safety laboratory tests [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH, FSH	X															
PK blood sample [9]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCSK9 measurement [10]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel [11]	X	X	X	X	X		X	X		X	X	X	X	X	X	X
Immunogenicity assessment			X [12]							X		X	X	X	X [13]	
Exploratory biomarkers [14]			X		X					X			X	X	X	
12-lead ECG [15]	X	X	X	X	X	X	X	X		X			X			X
Pregnancy test [16]	X															
Urine drug and alcohol screen [17]	X	X					X	X	X	X	X	X	X	X	X	X
Randomization			X													
Study drug administration			X													
Injection site assessment			X [18]	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

See footnotes on next page.

All blood samples, with the exception of those collected 8, 12 and 36 hours post-dose, should be collected while the subject is in a fasted state ( $\geq 10$  hours).

When multiple study procedures are scheduled at the same time point, the order of procedures should be as follows: perform ECG, obtain vital signs, and collect blood sample.

A  $\pm 2$ -day window is allowed for all post-confinement clinic visits.

A  $\pm 15$ -minute window for all post-dose procedures and blood draws and a  $\pm 30$  minute window for ECGs and physical examinations are allowed.

1. If the screening visit occurs on Day -1, the procedures from these visits will be combined. Subjects designated as 'reserve' and admitted on Day -1 but not required, or randomized, on Day 1 must undergo repeat Day -1 assessments to continue in the study, if  $>28$  days since screen visit a combined screen/Day -1 visit will be carried out.
2. Procedures will be performed at weekly intervals (Days 50, 57, 64 etc.) for subjects in the IV cohorts whose LDL-C levels have not return to within 20% of baseline. The baseline LDL-C for determining continued weekly visits if LDL-C is  $>20\%$  from baseline at Day 43 will be the lowest of the pre-dosed Friedewald calculated LDL-C (i.e. screening, Day -1 or Day 1). As Friedewald underestimates LDL-C  $<70$  mg/dL, post dose LDL-C will be by ultracentrifugation if LDL-C by Friedewald is  $>20\%$  from baseline.
3. Subjects will be confined for 72 hours post-dose; discharge from the unit is expected on the morning of Day 4.
4. Medical history will include all toxicities and allergies to previous treatments.
5. A physical examination is required in the 24 hours prior to study drug administration. If the screening visit and/or Day -1 physical examination was performed within 24 hours of study drug administration, it does not need to be repeated on Day 1. On Days 3 and 4, physical examinations should be performed at least 48 and 72 hours, respectively.
6. Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the subject has been seated or supine for  $\geq 5$  minutes. On Day 1, vital signs will be measured pre-dose, at 10 minutes (mid-infusion) and at the end of infusion, and at 2, 4, and 8 hours after termination of infusion.
7. Serology will include HIV, HB<sub>s</sub>Ag, and HCV screening.
8. Safety laboratory tests will include chemistry, hematology, and urinalysis.
9. On Day 1, PK blood samples will be collected pre-dose, at termination of infusion, and at 1, 2, 4, 8, and 12 hours after termination of infusion. Samples will also be collected at 24, 36, 48, and 72 hours from start of infusion.
10. Total and free PCSK9. On Day 1, blood samples for measurement of total and unbound (free) PCSK9 will be collected pre-dose and at 1, 2, 4, 8 and 12 hours after termination of infusion. Samples will also be collected at 24, 36, 48, and 72 hours from start of infusion.
11. The lipid panel includes LDL-C (calc by Friedewald and Hopkins formulas), TC, HDL-C, VLDL-C (calculated by Friedewald and Hopkins), TG. During confinement, blood samples for lipid measurement will be collected pre dose and at 4, 12, 24, 36, and 48 hours post-dose. Only TC, HDL-C, and TG will be measured, and Friedewald and Hopkins formulas used to calculate LDL-C and VLDL-C at these time points, and the remaining serum will be frozen at  $-70^{\circ}\text{C}$  for apolipoprotein measurements if needed. LDL-C and VLDL-C (measured by preparative ultracentrifugation) and apo B, apo A1, and Lp(a) will be measured on Days 1 (pre-dose), 8, 15, 29 and 43.
12. Blood samples for immunogenicity assessment will be collected pre-dose on Day 1.
13. Subjects with positive antibody results at Day 43 will return for follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator.
14. Exploratory biomarker blood samples will be collected and frozen for potential assessment of additional lipid or other biomarkers. During confinement, blood samples for exploratory biomarkers will be collected pre-dose and at 48 hours from start of infusion.
15. On Day 1, 12-lead (single) ECGs will be performed pre-dose and 10 minutes after termination of infusion, and at 1, 2, 4, and 8 hours after termination of infusion. Twelve-lead (single) ECGs will also be performed at 24 hours from the start of infusion and at least at 48, and 72 hours from start of infusion. Subjects should be resting in the supine position for  $\geq 10$  minutes prior to each 12-lead ECG.
16. A serum pregnancy test will be performed at screening on all women
17. Alcohol testing may be performed by urine screen or breath test at the same time points. Subjects who test positive for alcohol at screening, but have no history of alcohol abuse, must be negative on retest at least 48 hours prior to check in for Study Day -1 and again at Day -1.
18. On Day 1, injection site assessments will be performed pre-dose and 12 hours after termination of infusion.

apo = apolipoprotein; BMI = body mass index; ECG = electrocardiogram; ET = early termination; FUP = follow-up period; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

**Table 4. Timed Assessments During Confinement – Intravenous Dosing Cohorts**

Study Day	Day 1									Day 2		Day 3	Day 4
	0 hr (pre-dose)	10 min (mid- infusion)	end infusion	10 min post- infusion	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr	36 hr	48 hr	72 hr
Physical examination	X [1]												X
12-lead ECG [2]	X			X	X	X	X	X		X		X	X
Vital signs [3]	X	X	X			X	X	X		X		X	X
PK blood sample [4]	X		X		X	X	X	X	X	X	X	X	X
PCSK9 measurement [5]	X				X	X	X		X	X	X	X	X
Lipid panel [6]	X						X		X	X	X	X	
Immunogenicity assessment [7]	X												
Exploratory biomarkers [8]	X											X	
Study drug administration	X												
Injection site assessment	X								X	X		X	X

All blood samples, with the exception of those collected 8, 12 and 36 hours post-dose, should be collected while the subject is in a fasted state ( $\geq 10$  hours). When multiple study procedures are scheduled at the same time point, the order of procedures should be as follows: perform ECG, obtain vital signs, and collect blood sample.

A  $\pm 15$ -minute window for all post-dose procedures and blood draws and a  $\pm 30$  minute window for ECGs and physical examinations are allowed.

Subjects with positive antibody results at Day 43 will return for follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator.

Time points are relative to the start of the infusion.

1. A physical examination is required in the 24 hours prior to study drug administration. If the screening visit and/or Day -1 physical examination was performed within 24 hours of study drug administration, it does not need to be repeated on Day 1. On Days 3 and 4, physical examinations should be performed at least 48 and 72 hours, respectively.
2. On Day 1, 12-lead (single) ECGs will be performed pre-dose and 10 minutes after termination of infusion, and at 1, 2, 4, and 8 hours after termination of infusion. Twelve-lead (single) ECGs will also be performed at 24 hours from the start of infusion and at least at 48, and 72 hours from start of infusion. Subjects should be resting in the supine position for  $\geq 10$  minutes prior to each 12-lead ECG.
3. Vital signs will include blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the subject has been seated or supine for  $\geq 5$  minutes. On Day 1, vital signs will be measured pre-dose, at 10 minutes (mid-infusion) and at the end of infusion, and at 2, 4, and 8 hours after termination of infusion.
4. On Day 1, PK blood samples will be collected pre-dose, at termination of infusion, and at 1, 2, 4, 8, and 12 hours after termination of infusion. Samples will also be collected at 24, 36, 48, and 72 hours from start of infusion.
5. Total and free PCSK9. On Day 1, blood samples for measurement of total and unbound (free) PCSK9 will be collected pre-dose and at 1, 2, 4, 8 and 12 hours after termination of infusion. Samples will also be collected at 24, 36, 48, and 72 hours from start of infusion.
6. The lipid panel includes LDL-C (calc by Friedewald and Hopkins formulas), TC, HDL-C, VLDL-C (calculated by Friedewald and Hopkins), TG. During confinement, blood samples for lipid measurement will be collected pre dose and at 4, 12, 24, 36, and 48 hours post-dose. Only TC, HDL-C, and TG will be measured, and Friedewald and Hopkins formulas used to calculate LDL-C and VLDL-C at these time points, and the remaining serum will be frozen at  $-70^{\circ}\text{C}$  for apolipoprotein measurements if needed. LDL-C and VLDL-C (measured by preparative ultracentrifugation) and apo B, apo A1, and Lp(a) will be measured on Days 1 (pre-dose), 8, 15, 29 and 43.

7. Subjects with positive antibody results at Day 43 will return for follow-up assessment approximately every 28 days for antibody and immunological adverse event assessment until resolved or until judged to be chronic or stable by the Investigator.
  8. Exploratory biomarker blood samples will be collected and frozen for potential assessment of additional lipid or other biomarkers.
- apo = apolipoprotein; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PK = pharmacokinetics; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol.

## APPENDIX B: CLINICAL LABORATORY ANALYTES

### Standard Safety Chemistry Panel

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

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

**Fasting Lipid Panel** (LDL-C, and VLDL-C, will be calculated by Friedewald and Hopkins formulae whenever lipid panel is performed. Direct measurements by ultracentrifugation (BQuant) and Apo A1, B and Lp(a) will be only performed where specifically specified)

Apolipoprotein A1 <sup>2</sup>	Apolipoprotein B <sup>2</sup>
High-density lipoprotein cholesterol	Lipoprotein (a) <sup>2</sup>
Low-density lipoprotein cholesterol (LDL-C) (direct) [1]	Total cholesterol
Triglycerides	Very low-density lipoprotein cholesterol (VLDL-C)

1. At all visits including during confinement, blood samples for lipid measurement will be collected pre-dose and TC, HDL-C, and TG will be measured, and Friedewald and Hopkins formulas used to calculate LDL-C and VLDL-C at all time points. The remaining serum will be frozen at -70°C for apolipoprotein measurements if needed.
2. Low-density lipoprotein cholesterol and VLDL-C will also be measured by preparative ultracentrifugation and apos A1, B and Lp(a) measured on Days 1 (pre-dose), 8, 15, 29 and 43.

### Endocrinology

Follicle-stimulating hormone (FSH) [1]  
Thyroid-stimulating hormone  
Free thyroxine (FT4)

1. Post-menopausal is defined as women with amenorrhea ≥12 consecutive months without another cause and a documented serum FSH level >35 mIU/mL; or irregular menstrual periods and a documented serum FSH level >35 mIU/mL; or women on hormone replacement therapy.

### Serology

Serum for hepatitis C antibody, hepatitis B surface antigen (HB<sub>s</sub>Ag), HIV-1, -2 antibody (screening only)

### **Hematology**

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential (absolute and % differential)[1]	

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

### **Additional Hematology**

Mean corpuscular volume

### **Urinalysis**

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

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

### **Serum pregnancy test (for all women at screening) -**

### **Drugs of Abuse**

Amphetamine	Barbiturates
Benzodiazepines	Cocaine
Tetrahydrocannabinol	Opiates
Phencyclidine	

Alcohol testing may be performed by urine screen or breath test.