

STATISTICAL ANALYSIS PLAN

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

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Sponsor: LIB Therapeutics, LLC
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VERSION HISTORY

Version	Version Date	Description
1.0	14 May 2021	Original signed version
2.0	18 May 2023	Updates prior to database lock and prior to unblinding: • Section 3.1.3: Clarification of handling Day 1 for baseline. • Section 3.1.3: Remove lipid fasting requirement for analysis. • Section 3.1.6: Clarification of lab units to be used. • Section 3.1.7: Clarification of calculation for the mean of weeks 22 and 24. • Section 3.1.8 added to address other race groups. • Section 3.2: Clarification of using planned or actual treatment for each population. • Sections 3.2.1 and 3.2.2: Clarification of including subjects that discontinue study drug. • Section 3.2.3: Require all 6 doses for Per-Protocol Population. • Section 3.3.3: Add summary of baseline ezetimibe status. • Section 3.3.5: Add summary of concomitant lipid lowering therapies. • Section 3.4: text added for reflexive approach when LDL-C by Friedewald formula is missing. A similar approach is used when LDL-C by preparative ultracentrifugation is missing. • Section 3.4: Provide SAS option needed for assuming unequal variances in efficacy analyses. • Section 3.4.1.1: Add details and sample SAS code for sensitivity analysis 3. • Section 3.4.1.1: Add sensitivity analysis 4. • Section 3.4.2: Remove imputation of missing data for other secondary endpoints. Imputation for key secondary endpoints remains. • Section 3.7.1: Minor edits to the AE overview summary. • Section 3.7.1: Add summaries of administration site reactions. • Section 3.7.1: Add summary of TESAEs by SOC and PT, and by PT. • Section 3.7.2: Add shift table for fasting glucose levels and HbA1c levels (normal, prediabetes, and diabetes). • Global: Clarify throughout that CVD status from IRT, not EDC, will be used as a factor in analysis models. • Appendix A: Add sample SAS code. • Other minor edits as needed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical
apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
BMI	Body mass index
CEC	Clinical Endpoint Committee
CI	Confidence interval
CK	Creatine kinase
CKD	Chronic kidney disease
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
CVE	Cardiovascular events
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EL	Eligibility lipid
ESC	European Society of Cardiology
ET	Early Termination
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
IRT	Interactive response technology
ISR	Injection site reaction
ITT	Intent-to-Treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LLN	Lower limit of normal
Lp(a)	Lipoprotein (a)
mAb	Monoclonal antibody

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MMRM	Mixed-effect model repeated measurement
NAb	Neutralizing antibody
OLE	Open-label extension
OM-3	Omega-3 fatty acids
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
REML	Restricted maximum likelihood
Q2W	Every 2 weeks
Q4W (≤ 31 days)	Monthly
RL	Repeat lipid
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SCORE	Systematic Coronary Risk Estimation
SD	Standard deviation
SI	Système International
siRNA	Short interfering ribonucleic acid
T1DM	Type 1 diabetes mellitus
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TEAE	Treatment-emergent serious adverse event
TG	Triglycerides
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number LIB003-004. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

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

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

2.1.3 Exploratory Objectives

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

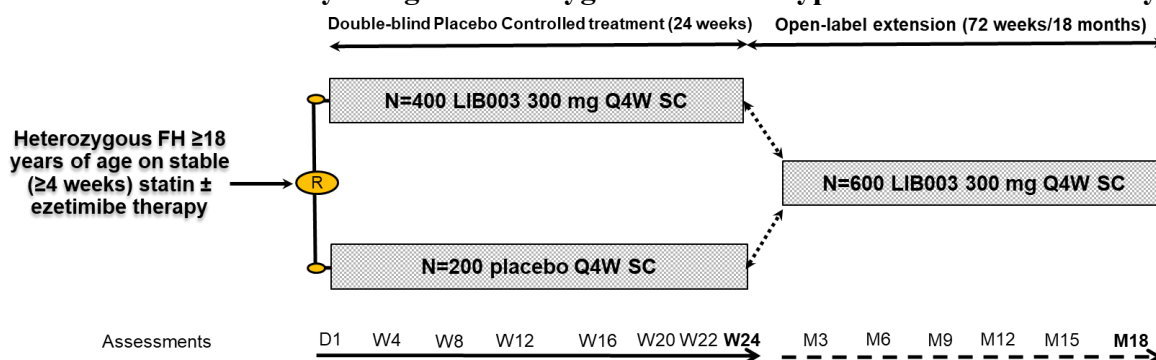
- To assess the LDL-C response based on underlying genetic variants associated with HeFH;
- To assess the effects on other lipid and cardiovascular (CV) risk biomarkers as appropriate.

2.2 Study Design

2.2.1 Overview

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

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



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

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

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

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

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

Table 1 below presents the schedule of procedures of the study.

TABLE 1. SCHEDULE OF PROCEDURES

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

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

A ±3-day window is permitted for all clinic visits, but **every attempt should be made to dose patients ≤31 days from prior dose** (not from Day 1); unanticipated or unavoidable cancellations due to weather or public holidays may be scheduled within a 5-day window and will not be considered protocol deviations if appropriately documented.

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

See Protocol Appendix B for a complete list of safety chemistry, lipid, hematology, and urinalysis analytes.

- These visits are only for patients who do not require washout and/or diet and lipid stabilization. Screening procedures must be performed no earlier than 5 days and no later than 21 days prior to commencing randomization and dosing on Day 1. Patients documented to have been on allowed oral lipid-lowering medication for ≥4 weeks and who have not received any PCSK9 mAb for the period specified in the inclusion/exclusion criteria (which is dependent on dose of mAb at screening) may proceed directly to randomization on Day 1.
- These visits are only for patients who do require washout and/or diet and lipid stabilization. Screening procedures must be performed no earlier than 5 days and no later than 77 days prior to commencing randomization and dosing on Day 1. For patients on a PCSK9 mAb at a dose of 75 mg, 140 mg, or 150 mg Q2W, the washout period is ≥4 weeks after the last dose, and for those on 300 mg or 420 mg Q4W (≤31 days) the washout period is ≥8 weeks following last dose (see inclusion/exclusion criteria in Protocol Section 4). For patients who have received an siRNA PCSK9 inhibitor, the washout period is ≥360 days post last dose. During the washout phase patients may have up to 2 additional clinic visits for assessment of inclusion/exclusion criteria.
- Patients on LIB003 who test positive for binding, non-NABs and have clinical sequelae that are considered safety-related at the final visit of this study (Day 169/Week 24/ET) may be asked to return for additional monthly follow-up testing if they terminate this study (LIB003-004) and do not enter the OLE study. Patients on LIB003 who test positive for NABs at the final visit of this study (Day 169/Week 24/ET), who do not enter the OLE study, and have no clinical sequelae, will be asked to return for follow-up testing every 3 months until either NABs are no longer detectable, considered stable, or the patient has been followed for a period of at least 12 months. For patients who test positive, but have not received active drug, follow-up testing will not be required.

4. The Investigator and Sponsor will receive lipid, PK and PCSK9 baseline measurements for Day 1. Measurements after Day 1 will be blinded to the Investigator and study personnel involved in the study at both the clinical site and LIB Therapeutics.
5. Patients whose LDL-C is up to 5 mg/dL below the defined entry level based on very-high risk for CVD or high risk for CVD or triglycerides >400 to 450 mg/dL may have 1 fasting lipid repeat profile (Screening Visit repeat lipid [RL]).
6. Patients who meet HeFH and other entry criteria but require washout of lipid-lowering agents excluded in the study (see inclusion/exclusion criteria in Protocol Section 4) and/or diet and allowed oral lipid-lowering drug stabilization (eg, statins, ezetimibe, bile acid sequestrants, OM-3, bezafibrate, fenofibrate, nicotinic acid, and bempedoic acid) will have a fasting lipid profile at the EL Visit to determine the final eligibility after completing the required washout/stabilization period.
7. Review inclusion and exclusion criteria.
8. Includes statin, statin dose, ezetimibe, and other oral lipid-lowering medications (bile acid sequestrants, nicotinic acid, bezafibrate, fenofibrate, OM-3 compounds, and bempedoic acid) plus adherence for 4 weeks; record prior treatment with evolocumab or alirocumab including dose, dosing frequency, and last dose. For Day 1/Week 0 verify the last dose of a PCSK9 mAb was ≥ 4 to 8 weeks ago.
9. Blood sample for DNA/genotyping of HeFH will be obtained at the randomization visit, if necessary.
10. TSH at screening. For patients with TSH <LLN or $>1.5 \times$ ULN an FT3 will be performed,
11. A urine pregnancy test will be performed only on females of childbearing potential. Serum FSH will be measured for women uncertain of postmenopausal status (<1 year since last menses) at screening only.
12. Serum will be collected for immunogenicity (ADAs), PCSK9, and PK at all Q4W visits for all patients. ADAs will be analyzed initially for LIB003 patients at Day 1 and Weeks 12 and Week 24/ET. PK will be analyzed at Weeks 12 and 24/ET and PCSK9 will be analyzed at Day 1 and Weeks 12 and 24/ET. Patients confirmed positive for LIB003 antibodies at Week 12 or Week 24/ET will be tested for NAb, PCSK9 (free), and PK at that visit. Previous visit samples may be analyzed as outlined above (immunogenicity, PCSK9, and PK) to better characterize the findings. Samples collected for placebo-treated patients will be stored for potential measurement.
13. Measured initially. Other time points analyzed to address positive ADAs or population PK plan (PK only).
14. Blood samples for exploratory biomarkers will be collected and frozen for potential assessment of additional lipid or CV risk biomarkers.
15. Height and body weight will be used to calculate BMI. BMI will be calculated only at screening.
16. Includes blood pressure, heart rate, respiratory rate, and temperature. Blood pressure and heart rate will be measured after the patient has been seated or supine for ≥ 5 minutes.
17. Patients should be resting in the supine position for ≥ 10 minutes prior to each 12-lead ECG.
18. On Day 1 and subsequent visits injection site assessments will be performed pre-dose and 15 minutes post-dose.
19. Patients will be reminded at all visits as to the importance of maintaining stability/adherence to their background medication and a low-fat, low cholesterol diet. Patients will be reminded at visits from Week 0 to Week 16 the importance of returning to the clinic in 28 days (≤ 31 days) for next dose of study drug. Patients will be reminded at Week 20 and Week 22 visits the importance of returning to the clinic in 14 days for the Week 22 and Week 24 visits, respectively.

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

2.2.2 Randomization and Blinding

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

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

2.2.3 Sample Size Determination

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

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoints

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

2.3.2 Secondary Efficacy Endpoints

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

- Percent change in:
 - LDL-C level at Week 24 (by Hopkins formula);
 - LDL-C level at Week 24 (by preparative ultracentrifugation); and
 - LDL-C level at mean of Weeks 22 and 24 (by Hopkins formula);

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

2.3.3 Immunogenicity Endpoints

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

2.3.4 Exploratory Efficacy Endpoints

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

2.3.5 Pharmacokinetic Endpoints

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

2.3.6 Safety Endpoints

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

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

For efficacy variables, scheduled visits will be assigned to analysis visits as recorded on the electronic case report form (eCRF). Unscheduled and early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Week 4	29	2	43
Week 8	57	44	71
Week 12	85	72	99
Week 16	113	100	127
Week 20	141	128	148
Week 22	155	149	162
Week 24	169	163	End of Study

Within an analysis visit window, if a scheduled visit occurs, then the measurement from this scheduled visit will be used as the measurement for the visit window. If no scheduled visit occurs within a visit window, the measurement from the visit closest to the scheduled visit within the visit window will be used. If there are more than one measurement with equal distance to the scheduled measurement, the last one will be used. If no visits occur within a visit window, the measurement for this visit will be treated as missing.

3.1.3 Definition of Baseline

Baseline for all efficacy and safety variables will be defined as Day 1. If the measurement at this visit is missing, the last measurement on or prior to the first dose date of study drug will be used. Note that if Day 1 is mistakenly collected post-dose on day 1, it will still be used for baseline.

While samples for lipids should be collected in a fasted state per Protocol, fasting is not required for statistical analysis of lipids.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation (SD), minimum, and maximum.

3.1.5 Handling of Dropouts and Missing Data

In cases of missing or incomplete dates (e.g. adverse event [AE] and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRF will be presented in the data listings.

Missing values for other variables will not be imputed and only observed values will be used in data analyses and summaries unless stated otherwise.

3.1.6 Units

Laboratory data will be listed and summarized using original conventional units as opposed to Système International (SI) units. Results using SI units will still be available in the database.

3.1.7 Mean of Weeks 22 and 24

The mean of weeks 22 and 24 will be calculated for LDL-C by Friedewald formula and LDL-C by Hopkins formula. For analyses in which missing data is imputed, weeks 22 and 24 will be imputed individually first and then the mean of weeks 22 and 24 will be calculated. For analyses using observed data without imputation, the mean of weeks 22 and 24 will be calculated even if only one of the visits is available.

3.1.8 Race

Race is collected as a dropdown menu (only one value may be selected) with the following options:

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Other, and then a free text field to specify

For the purpose of summary and analysis, including subgroups, subjects that have selected “Other” will be categorized into one of the five standard race designations where possible. This categorization will be documented and finalized prior to database lock. Both the original values and analysis categorizations will be listed. Where applicable in summaries, the number of subjects that originally selected “Other” but were then re-categorized will be noted.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

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

For ITT Population analysis, data will be used as observed regardless of whether the subject stopped study drug. See Per-Protocol Population for analysis excluding data if the drug dosing period from prior dose is more than 31 days.

Subjects in the ITT Population will be analyzed according to their randomized treatment group, even if they receive incorrect study drug.

3.2.2 *modified Intent-to-Treat (mITT) Population*

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

For mITT Population analysis, data will be used as observed regardless of whether the subject stopped study drug. See Per-Protocol Population for analysis excluding data if the drug dosing period from prior dose is more than 31 days.

Subjects in the mITT Population will be analyzed according to their randomized treatment group, even if they receive incorrect study drug.

3.2.3 *Per-Protocol (PP) Population*

The Per Protocol Population is defined as all mITT patients who receive all doses of study drug, have valid Week 24 LDL-C measurements, and have no major protocol deviations during the Treatment Period. Major protocol deviations that may impact the primary efficacy assessment may include but are not limited to:

- Missing LDL-C level at Week 24 (by Friedewald formula),
- Not completing at all 6 SC injections of the study drug,
- Using prohibited drugs or any products thought to alter the primary outcome variable during the study, or
- Any other major protocol deviation.

For the PP Population analysis, if the drug dosing period from the prior dose is more than 31 days, then this LDL-C measurement will not be considered as valid.

The Per Protocol Population will be used to assess the robustness of the primary efficacy analysis and the key secondary efficacy analysis results.

Potential subjects satisfying exclusion criteria will be listed and reviewed case by case with all data available. A list of subjects to be excluded from the Per Protocol Population will be finalized before database unblinding.

3.2.4 *Safety Population*

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

Subjects in the Safety Population will be analyzed according to the actual study drug received. If a subject randomized to placebo receives LIB003 even just once, they will be summarized in the LIB003 group for Safety Population summaries. If a subject randomized to LIB003 receives placebo, they will be summarized in the LIB003 group for Safety Population unless they received placebo for all doses.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will be summarized for all enrolled subjects for each treatment group and in total. The following subject disposition categories will be included in the summary:

- Subjects who were randomized,
- Subjects who received study drug,
- Subjects who completed the study, and
- Subjects who did not complete the study.

For subjects who did not complete the study, a summary will be provided by reason for discontinuation. In addition, the total number of subjects for each defined analysis population will be tabulated by treatment group.

Subject disposition data will be presented in a data listing.

3.3.2 Protocol Deviations

CSR-reportable protocol deviations as defined in the Medpace Protocol Deviation Plan will be summarized for the Safety Population. The number and percentage of subjects meeting any criteria will be summarized by treatment group and total. In addition, the protocol deviations related to COVID-19 will be categorized and summarized separately.

A data listing will be provided by subject.

3.3.3 Demographic and Baseline Characteristics.

Demographic and baseline characteristics will be summarized descriptively by treatment group and total for each analysis population:

- Age (years) at informed consent and age categories (<65 years, ≥65 years)
- Sex
- Race
- Ethnicity
- Weight
- Height
- Body mass index (BMI)
- Baseline LDL-C level calculated by Friedewald formula ($\leq$ median, $>$ median)
- Baseline LDL-C level calculated by Friedewald formula (Quartiles)
- Baseline LDL-C level calculated by Friedewald formula
- Baseline LDL-C level calculated by Hopkins formula
- Baseline LDL-C level calculated by preparative ultracentrifugation
- Baseline TC level
- Baseline HDL-C level
- Baseline non-HDL-C level
- Baseline VLDL-C level
- Baseline TG level

- Baseline serum unbound (free) PCSK9 concentrations
- Baseline statin intensity (high intensity [rosuvastatin 20 or 40 mg, or atorvastatin 40 or 80 mg], not high intensity)
- Baseline ezetimibe status (yes, no)
- Baseline diabetes status (yes, no)
- Baseline diabetes status (normal, prediabetes, diabetes)
- Diagnosis of HeFH (yes, no)
- Genotype status (confirmed, unconfirmed)
- Genetic variants (Low-density lipoprotein receptor [LDLR], PCSK9, Apo B, other)
- CVD status (no, very-high risk for CVD, high risk for CVD)
- CVD status from IRT (very-high risk for CVD, high risk for CVD)

For subjects with very-high risk CVD:

- Documented atherosclerotic cardiovascular disease (ASCVD) (yes, no),
- DM with target organ damage, or at least 3 major risk factors, or early onset of type 1 diabetes mellitus (T1DM) of long duration (yes, no),
- Severe chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) (yes, no),
- A calculated Systematic Coronary Risk Estimation (SCORE) 10% for 10-year risk of fatal CVD (yes, no), and
- FH with ASCVD or with another major risk factor (yes, no).

For subjects with high risk CVD:

- Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or blood pressure 180/110 mmHg (yes, no),
- Patients with FH without other major risk factors (yes, no),
- Patients with diabetes mellitus without target organ damage, with diabetes mellitus duration 10 years or another additional risk factor (yes, no),
- Moderate CKD (eGFR 30-59 mL/min/1.73 m²), and
- A calculated SCORE 5% and <10% for 10-year risk of fatal CVD (yes, no).

Categorical demographic variables will be summarized using frequency counts and percentages. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum).

3.3.4 Medical History

Medical history will be coded to system organ class and preferred term using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment group and in total using the ITT Population.

3.3.5 Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization Drug Dictionary (WHO Drug Sept 2020G B3). For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study drug and concomitant medications if they were taken at any time

after the first dose of study drug (i.e. started prior to the first dose of study drug and were ongoing or started after the first dose of study drug).

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment group and in total based on the Safety Population. Concomitant lipid lowering therapies will be summarized in a similar manner.

3.3.6 *Study Drug Exposure and Compliance*

Days of exposure to study drug will be calculated as date of last dose of study drug – date of first dose of study drug + 1. Note that the exposure calculation is intended to describe the length of time a subject was exposed to study drug and therefore does not take study drug interruptions into account. Days of exposure to study drug will be summarized by treatment based on the Safety Population with descriptive statistics and with counts and percentages of subjects with exposure in the following categories:

- ≤ 8 weeks (1 to 57 days),
- > 8 to ≤ 16 weeks (58 to 113 days), and
- > 16 weeks (≥ 114 days).

The number of SC injections for each subject will be summarized with counts and percentages by treatment group and in total on the Safety Population.

3.4 **Efficacy Assessment**

The efficacy analysis will be performed based on the ITT Population unless otherwise stated. Baseline values, as well as the actual change and percent change from baseline for the efficacy parameters will be summarized with descriptive statistics at each analysis visit by treatment group.

The primary endpoint of LDL-C by Friedewald formula will use a reflexive LDL-C approach when LDL-C by Friedewald is missing. The following hierarchical steps will be used:

1. Use LDL-C by preparative ultracentrifugation if available in place of missing LDL-C by Friedewald formula.
2. If both LDL-C by Friedewald and preparative ultracentrifugation unavailable, use LDL-C by Hopkins formula if available in place of missing LDL-C by Friedewald formula.
3. If all three LDL-C are missing (Friedewald, preparative ultracentrifugation, and Hopkins) then substitute “1” as the data point for LDL-C by Friedewald formula.

Situations where these steps are to be used for missing LDL-C by Friedewald include:

- LDL-C by Friedewald cannot be calculated due to triglycerides > 400 mg/dL.
- There was not enough sample volume to perform preparative ultracentrifugation.
- LDL-C by Friedewald cannot be calculated due to a result of negative or 0.

In analysis of secondary endpoint LDL-C by preparative ultracentrifugation, if LDL-C by preparative ultracentrifugation is missing then it will be substituted with LDL-C by Friedewald formula.

3.4.1 Primary Efficacy Endpoints

Primary Analysis

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

The statistical hypotheses for the co-primary endpoint of percent change from baseline in LDL-C level at Week 24 (by Friedewald formula) is the following:

$$H_0: \mu_1 - \mu_2 = 0$$

$$H_a: \mu_1 - \mu_2 < 0$$

where μ_1 and μ_2 are the mean percent change (reduction) in LDL-C level at Week 24 (by Friedewald formula) of LIB003 and Placebo, respectively.

The statistical hypotheses for the co-primary endpoint of percent change from baseline in LDL-C level at the mean of Weeks 22 and 24 (by Friedewald formula) is the following:

$$H_0: \mu_3 - \mu_4 = 0$$

$$H_a: \mu_3 - \mu_4 < 0$$

where μ_3 and μ_4 are the mean percent change (reduction) in LDL-C level at the mean of Weeks 22 and 24 (by Friedewald formula) of LIB003 and Placebo, respectively.

The family-wise type I error rate is controlled at a two-sided significance level of $\alpha=0.05$ by using a fallback procedure.

Under the fallback procedure, the percent change from baseline compared to placebo in LDL-C level at Week 24 (by Friedewald formula) will be tested first with two-sided significance level of $\alpha=0.05$. If the null hypothesis is rejected at a two-sided significance level of $\alpha=0.05$ and superiority of LIB003 over placebo is claimed, then this α is unused and is passed to the second primary endpoint test. The second primary endpoint of the percent change from baseline in LDL-C level at the mean of Weeks 22 and 24 (by Friedewald formula) will be tested with a two-sided significance level of $\alpha=0.05$.

Percent change from baseline in LDL-C will be analyzed with analysis of covariance (ANCOVA) model with treatment and the CVD status from IRT as the factors and baseline value as a covariate, assuming unequal variances between groups (Welch's Test, i.e. using the SAS option "ddfm=satterth"). For patients in the ITT Population who withdraw early, a multiple imputation washout model will be used. Missing baseline will not be statistically imputed; no missing baseline is expected.

See Appendix A for more details on this analysis.

3.4.1.1 Sensitivity Analysis for Primary Efficacy Endpoints

Sensitivity Analyses 1

A sensitivity analysis will be performed for the primary endpoint using Mixed-effect Model Repeat Measurement (MMRM) without multiple imputation and under the assumption of MAR with percent change in LDL-C from baseline to post-baseline visits (Week 4, Week 8, Week 12, Week 16, Week 20, Week 22 and Week 24) as a dependent variable, treatment, CVD status from IRT and analysis visit as the factors, baseline LDL-C and the interaction between treatment and analysis visit as covariates. Analysis visit will be the repeated term in the MMRM. The treatment difference at Week 24 will be estimated from the MMRM model.

Sensitivity Analyses 2

A tipping point analysis will be performed to search for the tipping point that reverses the study conclusion. In the tipping point analysis, we will independently vary the deltas in the treatment groups (LIB003 group progressively worse while the placebo group is not impacted and LIB003 group progressively worse while the placebo group progressively improves) until the hypothesis test on the co-primary efficacy endpoint becomes statistically insignificant.

Sensitivity Analyses 3

A rank analysis of variance (ANOVA) (Quade test) without multiple imputation will be used for patients who adhered to the scheduled study drug administration with visits ≤ 31 days and did not have any missing data for the coprimary endpoints (i.e. using the Per-Protocol Population).

This analysis is performed by ranking each dependent variable (percent change from baseline) and covariate (baseline value) using PROC RANK, ignoring treatment groups, using average ranks in case of ties, and ranking from the smallest first. Then run a linear regression of the ranks of the dependent variable on the ranks of the covariates, saving the residuals, again ignoring treatment groups. Using the residuals, an ANOVA will be performed with the residuals from the above step as the dependent variable and treatment and CVD status from IRT as factors; see sample SAS code below.

```
*****
Residual = Output dataset from PROC REG
CVDSTRAT = CVD status from IRT
TRTN = 1 (Placebo) or 2 (LIB003)
RESID = Residuals from PROC REG
*****;;
proc mixed data=residual;
  class TRT CVDSTAT;
  model RESID = TRT CVDSTAT;
run;
```

The Quade test of treatment group p-value using F distribution will be provided. Other statistics provided will be descriptive, including median, first and third quartiles, and interquartile range, and minimum and maximum.

Sensitivity Analysis 4

A similar multiple imputation model as for the primary analysis will be used, but assuming a shift towards baseline at a reduced rate for the LIB003 treatment group rather than a full return to baseline. See the end of Appendix A for details.

3.4.1.2 Supportive Analysis for Primary Efficacy Endpoints

The primary efficacy analysis will be repeated on the mITT Population and Per-Protocol Population.

3.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints will not be tested if either one of the co-primary efficacy endpoints' null hypothesis fails to be rejected.

The key secondary endpoints of this study are:

Percent change in:

- LDL-C level at Week 24 (by Hopkins formula);
- LDL-C level at Week 24 (by preparative ultracentrifugation); and
- LDL-C level at mean of Weeks 22 and 24 (by Hopkins formula);

The Hochberg procedure [Hochberg, 1988]¹ will be applied to control the family-wise type I error rate at a two-sided significance level of $\alpha=0.05$ for the key secondary endpoints.

Under Hochberg procedure, the two-sided p-values are sorted. The endpoint with the largest p-value is compared to its alpha critical value of $\alpha=0.05$. If the null hypothesis is rejected at a two-sided significance level of $\alpha=0.05$, then superiority of LIB003 over placebo is claimed for all the key secondary endpoints. If the null hypothesis is not rejected, continue to the second step, the second largest p-value is compared to $\alpha/2=0.025$. If the null hypothesis is rejected at a two-sided significance level of $\alpha/2=0.025$, then superiority of LIB003 over placebo is claimed for all the key secondary endpoints except for the one associated with the largest p-value. If the null hypothesis is not rejected, then continue to the third step, the next largest p-value is compared to $\alpha/3=0.0167$. If the null hypothesis is rejected at a two-sided significance level of $\alpha/3=0.0167$, then superiority of LIB003 over placebo is claimed for the third key secondary endpoints.

The key secondary efficacy endpoints will be analyzed with analysis of covariance (ANCOVA) model with treatment and the CVD status from IRT as the factors and baseline value as a covariate, assuming unequal variances between groups (Welch's Test, i.e. using the SAS option "ddfm=satterth") and the same imputation method will be used as the primary efficacy endpoints.

See Appendix A for more details on this analysis.

The analysis will be repeated on mITT and PP Populations.

The other secondary endpoints of this study are:

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

Other secondary endpoints of other lipids (TC, HDL-C, non-HDL-C, VLDL-C, and TG), serum unbound (free) PCSK9, apo B and Lp(a) at Week 24 will be analyzed using the analysis of covariance (ANCOVA) model with treatment and the CVD status from IRT as the factors and baseline value of efficacy measurement of interest as a covariant, assuming unequal variances between groups (Welch's Test, i.e. using the SAS option "ddfm=satterth"). Only observed data will be used; missing data will not be imputed.

See Appendix A for more details on this analysis.

Absolute and percent change from baseline (Day 1) in LDL-C level by Friedewald and Hopkins formulas at all visits (Weeks 4, 8, 12, 16, 20, 22, and 24) will be summarized with descriptive statistics at each analysis visit by treatment group. The above summary will be repeated for TC, HDL-C, non-HDL-C, VLDL-C, TG, apo B and Lp(a). Serum unbound (free) PCSK9 concentrations will be summarized with descriptive statistics at each analysis visit by treatment group.

Percentage of patients achieving current ESC/EAS guidelines will be analyzed using logistic regression model with treatment and the CVD status from IRT as the factors and baseline value as a covariate. The odds ratio and 95% confidence interval for the odds ratio will be provided.

3.4.3 Exploratory Endpoints

The exploratory endpoints of this study are:

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

Descriptive statistics of the baseline, change from baseline and percent change from baseline (Day 1) in LDL-C level to Week 24 will be presented by HeFH variant and treatment group.

If the data permits, descriptive statistics of the baseline, change from baseline and percent change on other lipid and cardiovascular risk biomarkers after multiple doses will be presented by treatment group.

3.4.4 Subgroups

Analyses of co-primary efficacy endpoints and key secondary endpoints will be performed using the same approach as specified above for the primary and key secondary endpoints for subgroups of patients based on baseline characteristics for the following if data permits:

- Age group (<65 years, ≥65 years)
- Sex (male, female)
- BMI (≤ median, > median)
- Race (Black or African American, White, other)
- Baseline LDL-C level calculated by Friedewald formula (≤ median, > median)
- Baseline LDL-C level calculated by Friedewald formula (Quartiles)
- Baseline statin intensity (high intensity, not high intensity)
- Baseline diabetes status (yes, no)
- Baseline diabetes status (normal, prediabetes, diabetes)
- Diagnosis of HeFH (yes, no)
- Genotype status for those diagnosed with HeFH (confirmed or unconfirmed)
- CVD status from IRT (very-high risk, high risk)

Any additional subgroup may be considered.

Treatment-emergent AEs will be summarized within each of subgroup above.

3.5 Immunogenicity Assessment

The number and percentage of subjects with positive ADA results will be counted for each time point and overall by treatment, and the immunogenicity data will be listed by treatment for the ITT Population.

3.6 Pharmacokinetic Assessment

The PK concentration for LIB003 will be summarized descriptively for the ITT Population.

3.7 Safety Assessment

Safety data will be summarized by actual treatment received and in total based on the Safety Population. In the event that a subject takes the wrong study drug (i.e. did not take the randomized study drug), the actual treatment received will be used for safety analyses.

3.7.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class and preferred term using MedDRA version 23.1.

Treatment-emergent adverse events (TEAEs) are defined as AEs that start on or after the first dose date of study drug.

For this study, Adverse events of special interest (AESIs) include the following:

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

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

An overview of AEs will be provided including counts and percentages of subjects with the following:

- Any TEAEs (overall and by maximum severity)
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs of special interest (overall and by maximum severity)
- Any TEAEs of administration site reaction
- Any serious treatment-emergent AEs (TESAEs)
- Any study drug related TESAEs (overall and by maximum severity)
- Any TESAEs of special interest (overall and by maximum severity)
- Any TEAEs leading to withdrawal of study drug
- Any TEAEs leading to discontinuation of study
- Any TEAEs leading to death
- Any TEAEs related to COVID-19
- Any TEAEs related to COVID-19 vaccine

The number and percentage of subjects who experienced at least one TEAE will be presented by system organ class and preferred term. Drug-related TEAEs, TESAEs, study drug withdrawal due to TEAEs, and study discontinuations due to TEAEs will be summarized in the same manner.

Summaries will be provided by maximum severity for the number and percentage of subjects with TEAEs and for subjects with drug-related TEAEs by system organ class and preferred term.

TEAEs, TEAEs of administration site reactions, and TESAEs will be summarized by preferred term.

Although a subject may have two or more TEAEs, the subject is counted only once within a system organ class and preferred term. The same subject may contribute to two or more preferred terms in the same system organ class or to two different system organ classes.

For AEs and SAEs of special interest, risk difference along with 95% confidence intervals will be presented to compare treatment groups.

A list of subjects who have serious AEs (SAEs), a list of subjects who withdrawal study drug due to AEs, a list of subjects who discontinue from study drug due to AEs, and a list of TEAEs leading to death will be provided. All AEs will be listed.

3.7.2 Clinical Laboratory Tests

Descriptive statistics of each hematology, serum chemistry, and urinalysis parameter will be presented for baseline, 'Time point', and change from baseline to each 'Time point'; where 'Time Point' is each post-baseline assessment. These will be presented by treatment group for the Safety Population.

Counts and percentages of subjects with any post-baseline observation that is below the lower limit of normal ($\leq$ LLN) or above the upper limit of normal ($>$ ULN) will be summarized for each hematology and serum chemistry parameter by treatment group and total.

Shifts from baseline to worst post-baseline value will be presented for specified lab tests (ALT, AST, CK, total bilirubin) by treatment group and total. Results will be categorized based on the criteria in the table below.

Parameter	Categories			
ALT	$\leq 1 \times \text{ULN}$	$> 1 \times \text{ULN}$ to $\leq 2 \times \text{ULN}$	$> 2 \times \text{ULN}$ to $\leq 3 \times \text{ULN}$	$> 3 \times \text{ULN}$
AST	$\leq 1 \times \text{ULN}$	$> 1 \times \text{ULN}$ to $\leq 2 \times \text{ULN}$	$> 2 \times \text{ULN}$ to $\leq 3 \times \text{ULN}$	$> 3 \times \text{ULN}$
CK	$\leq 1 \times \text{ULN}$	$> 1 \times \text{ULN}$ to $\leq 5 \times \text{ULN}$	$> 5 \times \text{ULN}$ to $\leq 10 \times \text{ULN}$	$> 10 \times \text{ULN}$
Total Bilirubin	$\leq 1 \times \text{ULN}$	$> 1 \times \text{ULN}$ to $\leq 1.5 \times \text{ULN}$	$> 1.5 \times \text{ULN}$ to $\leq 2 \times \text{ULN}$	$> 2 \times \text{ULN}$

The number and percentage of subjects who meet ALT or AST $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$ at any time after the first dose of the study drug will be identified as potential Hy's Law cases and summarized, and these subjects' ALT, AST and total bilirubin data will be listed.

A shift table of fasting glucose levels and baseline vs the highest post-dose level in each treatment group will be provided using the following categories:

- < 100 mg/dL (Normal)
- ≥ 100 and < 126 mg/dL (Prediabetes)
- ≥ 126 mg/dL (Diabetes)

A shift table of HbA1c levels and baseline vs the highest post-dose level in each treatment group will be provided using the following categories:

- $< 5.7\%$ (Normal)
- ≥ 5.7 to $< 6.5\%$ (Prediabetes)
- $\geq 6.5\%$ (Diabetes)

3.7.3 *Vital Signs*

Vital signs parameters (weight, body mass index, blood pressure, heart rate, respiratory rate, and temperature) will be summarized using descriptive statistics for the Safety Population by visit for each treatment group. The changes from baseline will also be presented.

A listing of all vital signs will be provided by subject.

3.7.4 *12-Lead Electrocardiograms*

ECG parameters (heart rate, PR, QRS, QT, QTcF, and RR) will be summarized using descriptive statistics at baseline, Week 24/ET by treatment group for the Safety Population. The overall interpretation will be summarized by counts and percentages by treatment group and total.

All ECG measurements and the overall interpretation will be listed by subject.

3.7.5 *Injection Site Reaction Assessments*

The number and percentage of subjects with injection site reactions will be summarized by reaction type and the intensity (mild, moderate and severe) by visit for each treatment group and total.

Injection site assessment data will also be listed.

3.7.6 *Deaths and CVEs*

Deaths and CVEs will be collected and will be adjudicated by an independent clinical endpoint committee (CEC). Events that are adjudicated as a “CVE” will be summarized by treatment group and total.

Deaths and CVEs data will also be listed.

4 DATA SAFETY MONITORING BOARD

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

5 INTERIM ANALYSIS

No interim analysis is planned for this study.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Percent change from baseline in LDL-C will be analyzed with analysis of covariance model with treatment as a factor and baseline value as a covariate. Since the patients will be stratified based on very-high risk for CVD or high risk for CVD to ensure balance across treatment groups, percent

change from baseline in LDL-C will be analyzed with analysis of covariance (ANCOVA) model with treatment and the CVD status as the factors and baseline value as a covariate.

The key secondary efficacy endpoints are specified in SAP.

Approximately 600 patients were to participate in this clinical study, including 400 to receive LIB003 and 200 to receive placebo. However, it is the Sponsor's decision to end enrollment with 478 patients randomized.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS[®] version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: MULTIPLE IMPUTATION WASHOUT MODEL

A multiple imputation washout model will be used for the coprimary efficacy analysis of the percent change from baseline compared to placebo in LDL-C level at Week 24 (by Friedewald formula) and LDL-C level at the mean of Weeks 22 and Week 24 (by Friedewald formula). The washout model can be considered as a modified control-based Pattern-Mixture Model (PMM) under the assumption of missing not at random (MNAR) for subjects who discontinued the study. For subjects who discontinued the study on LIB003 group, the missing values will be imputed with the observed baseline under the assumption that their outcome would be the similar to those in the placebo group. No intermediate values from LIB003 group should be used in the imputation for subjects in the LIB003 group. For subjects on placebo group, the intermediate missing values at the timepoints of interest will be imputed from the completers in the placebo group based on the missing at random (MAR) assumption.

The missing data will be imputed using the following steps.

For LIB003 group, the covariate and the baseline characteristics will be included in a multiple imputation procedure (SAS PROC MI) and will include the following.

- Baseline value of efficacy measurement
- Observed value of efficacy measurement for the timepoint of interest (Week 22 or Week 24) from the placebo group
- CVD status from IRT (very-high risk for CVD, high risk for CVD)

For placebo group, the covariate will be included in a multiple imputation procedure (SAS PROC MI) and will include the following.

- Baseline value of efficacy measurement
 - Observed value of efficacy measurement at Week 4 from the placebo group
 - Observed value of efficacy measurement at Week 8 from the placebo group
 - Observed value of efficacy measurement at Week 12 from the placebo group
 - Observed value of efficacy measurement at Week 16 from the placebo group
 - Observed value of efficacy measurement at Week 20 from the placebo group
 - Observed value of efficacy measurement at Week 22 from the placebo group
 - Observed value of efficacy measurement at Week 24 from the placebo group
 - CVD status from IRT (very-high risk for CVD, high risk for CVD)
1. Intermittent missing data (Weeks 4, 8, 12, 16 and 20) in the placebo treatment group will be imputed using MCMC methods, assuming MAR. Only subjects in the placebo group will be utilized in this step. SAS PROC MI will be utilized for this step using the MCMC

impute=monotone option. A total of 100 datasets will be created. These datasets will be utilized in Step #2. Sample SAS code is provided below.

```
proc mi data=xxxxx out=miout1 nimpute=100 seed=110000;  
  mcmc impute=monotone;  
  var Baseline Week_4 Week_8 Week_12 Week_16 Week_20;  
run;
```

2. The remaining missing values (Weeks 22 and 24) in the placebo group with a monotone missing data pattern will be imputed in this step. Missing data will be imputed assuming data are MAR. Only subjects in the placebo group will be utilized in this step. SAS PROC MI will be used to impute missing values utilizing the monotone reg option. This will be performed for the 100 datasets. After this step, the 100 datasets will be fully imputed for the placebo treatment group. These datasets will be utilized in Step #3. Sample SAS code is provided below.

```
proc mi data=miout1 out=miout2 nimpute=1 seed=110000;  
  by _Imputation_;  
  class CVDSTRAT;  
  var CVDSTRAT Baseline Week_4 Week_8 Week_12 Week_16 Week_20 Week_22;  
  monotone reg(Week_22/details);  
run;  
proc mi data= miout2 out=miout3 nimpute=1 seed=110000;  
  by _Imputation_;  
  class CVDSTRAT;  
  var CVDSTRAT Baseline Week_4 Week_8 Week_12 Week_16 Week_20 Week_22  
Week_24;  
  monotone reg(Week_24 /details);  
run;
```

3. Subjects in the LIB003 group who have the Week 22 value missing will be imputed in this step. Control-based PMM imputation will be performed. With this imputation model, the missing efficacy measurements in the LIB003 group will be imputed from the observed and imputed data in the placebo group at Week 22. Baseline data will also be utilized in the imputation. The MNAR statement in SAS PROC MI will be used to impute missing values. This will be performed for the 100 datasets. Sample SAS code is provided below.

```
proc mi data=yyyyy out=miout4 nimpute=1 seed=110000;  
  by _Imputation_;  
  class TRT01P CVDSTRAT;  
  var CVDSTRAT Baseline Week_22;  
  monotone reg (Week_22 /details);  
  mnar model(Week_22 / modelobs= (TRT01P='Placebo'));  
run;
```

4. Subjects in the LIB003 group who have the Week 24 value missing will be imputed in this step. Control-based PMM imputation will be performed. With this imputation model, the missing efficacy measurements in the LIB003 group will be imputed from the observed and imputed data in the placebo group at Week 24. Baseline data will also be utilized in the imputation. The MNAR statement in SAS PROC MI will be used to impute missing values. This will be performed for the 100 datasets. Sample SAS code is provided below.

```
proc mi data=miout4 out=miout5 nimpute=1 seed=110000;  
  by _Imputation_;  
  class TRT01P CVDSTRAT;
```

```
var CVDSTRAT Baseline Week_24;  
monotone reg (Week_24 /details);  
mnar model(Week_24 / modelobs= (TRT01P='Placebo'));  
run;
```

5. A total of 100 fully imputed datasets will be created (M=100). Since multiple imputation is a stochastic method, slight differences in output can be expected for different initial states of the random number generator. The seed numbers (seed=110000) will be identified in the SAS programs to allow for reproducibility.
6. After the missing data imputation is completed using the above steps, absolute change/percentage change values will be calculated in each of the imputed datasets at each visit and the mean of Weeks 22 and 24.
7. These 100 datasets will be analyzed using ANCOVA models with fixed effect of treatment group and the CVD status from IRT as factors, and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to Week 24 primary efficacy endpoint. Sample SAS code is provided below.

```
proc mixed;  
by PARAM _IMPUTATION_;  
class TRT01P(Ref='Placebo') CVDSTRAT;  
model PCHG = TRT01P CVDSTRAT Baseline / ddfm=satterth;  
lsmeans TRT01P / cl diff;  
run;
```

8. Similarly, these 100 datasets will be analyzed using ANCOVA models with fixed effect of treatment group and the CVD status from IRT as factors, and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to the mean of Weeks 22 and 24 primary efficacy endpoint.
9. Treatment effects (difference in LS means between treatments) from these 100 analyses will then be combined using Rubin's Method via SAS PROC MIANALYZE procedure for each endpoint.

Note: Since LDL-C by preparative ultracentrifugation is only collected at Baseline and Week 24, the multiple imputation steps will be modified as follows:

1. Step 1 is skipped (imputation of intermittent missing data [Weeks 4, 8, 12, 16 and 20] in the placebo group).
2. Missing Week 24 values in the placebo group will be imputed in this step. Missing data will be imputed assuming data are MAR. Only subjects in the placebo group will be utilized in this step. SAS PROC MI will be used to impute missing values utilizing the monotone reg option. This will be performed for the 100 datasets. After this step, the 100 datasets will be fully imputed for the placebo treatment group. These datasets will be utilized in Step #4. Sample SAS code is provided below.

```
proc mi data=xxxxx out=miout3 nimpute=100 seed=110000;  
class CVDSTRAT;  
var CVDSTRAT Baseline;  
monotone reg(Week_24 /details);  
run;
```

3. Step 3 is skipped (imputation of Week 22 in the LIB003 group).
4. Steps 4 onward are similar to the primary analysis.

Sensitivity Analysis 4

For sensitivity analysis, the primary analysis imputation model will be modified as follows:

1. Intermittent missing data (Weeks 4, 8, 12, 16 and 20) in the placebo treatment group will be imputed using MCMC methods, assuming MAR. Only subjects in the placebo group will be utilized in this step, similar as for the primary analysis imputation.
2. The remaining missing values (Weeks 22 and 24) in the placebo group with a monotone missing data pattern will be imputed in this step, similar as for the primary analysis imputation.
3. Intermittent missing data (Weeks 4, 8, 12, 16 and 20) in the LIB003 treatment group will be imputed using MCMC methods, assuming MAR. Only subjects in the LIB003 group will be utilized in this step. SAS PROC MI will be utilized for this step using the MCMC impute=monotone option. A total of 100 datasets will be created. These datasets will be utilized in Step #4. Sample SAS code is provided below.

```
proc mi data=xxxxx out=miout1b nimpute=100 seed=110000;  
  where TRT01P='LIB003 300 mg'  
  mcmc impute=monotone;  
  var Baseline Week_4 Week_8 Week_12 Week_16 Week_20;  
run;
```

4. Once the intermittent missing data is imputed and a monotone missing pattern is achieved for weeks 4 – 20, the remaining missing values for subjects in the LIB003 group will be imputed. The calculation will be done using the observed or imputed value of the prior visit, and a shift of -4.5% for missing Week 22 if the subject dosed at Week 20, and a shift of 10.8% toward baseline for all others. The 10.8% return to baseline model assumes that LIB003 subjects have the LDL-C values increase at a rate of 10.8% per week after last dose. Sample SAS code is provided below.

```
data miout2b;  
  set miout1b;  
  Rate1=0.108;  
  Rate2=-0.045;  
  if Week_4=. then Week_4 = Baseline;  
  if Week_8=. then Week_8 = Week_4 + 4*Rate1*Baseline;  
  if Week_12=. then Week_12 = Week_8 + 4*Rate1*Baseline;  
  if Week_16=. then Week_16 = Week_12 + 4*Rate1*Baseline;  
  if Week_20=. then Week_20 = Week_16 + 4*Rate1*Baseline;  
  if Week_22=. & DosedW20='Y' then Week_22 = Week_20 + 2*Rate2*Baseline;  
  else if Week_22=. then Week_22 = Week_20 + 2*Rate1*Baseline;  
  if Week_24=. then Week_24 = Week_22 + 2*Rate1*Baseline;  
run;
```

5. The remaining steps are similar to the primary analysis. A total of 100 fully imputed datasets will be created (M=100). Since multiple imputation is a stochastic method, slight differences in output can be expected for different initial states of the random number generator. The seed numbers (seed=110000) will be identified in the SAS programs to allow for reproducibility.

6. After the missing data imputation is completed using the above steps, absolute change/percentage change values will be calculated in each of the imputed datasets at each visit and the mean of Weeks 22 and 24.
7. These 100 datasets will be analyzed using ANCOVA models with fixed effect of treatment group and the CVD status from IRT as factors, and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to Week 24 primary efficacy endpoint. Sample SAS code is provided below.
8. Similarly, these 100 datasets will be analyzed using ANCOVA models with fixed effect of treatment group and the CVD status from IRT as factors, and baseline LDL-C as a covariate for the percent change of LDL-C from baseline to the mean of Weeks 22 and 24 primary efficacy endpoint.
9. Treatment effects (difference in LS means between treatments) from these 100 analyses will then be combined using Rubin's Method via SAS PROC MIANALYZE procedure for each endpoint.

APPENDIX B: REFERENCES

1. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75:800-2. Protocol MDCO-PCS-17-08 Amendment 2