STATISTICAL ANALYSIS PLAN

Protocol Title:	**Open-Label Extension, Phase 2b Study to Evaluate the Longer Term Efficacy and Safety of LIB003 in Patients on Stable Lipid-Lowering Therapy Requiring Additional LDL-C Reduction**
Protocol Number:	LIB003-010
Protocol Version/Date:	2.0, 10 September 2019
Investigational Product:	LIB003
Sponsor:	LIB Therapeutics, LLC 5375 Medpace Way Cincinnati, OH 45227
SAP Version/Date:	1.0, 20 January, 2020

SIGNATURE PAGE

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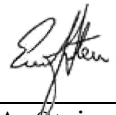

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VERSION HISTORY

Version	Version Date	Description
1.0	20 January 2020	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
apo	Apolipoprotein
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CK	Creatine kinase
CSR	Clinical study report
ECG	Electrocardiogram
HDL-C	High-density lipoprotein cholesterol
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
LLN	Lower limit of normal
NAb	Neutralizing antibody
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic
PK	Pharmacokinetic
Q4W	Every 4 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

1 INTRODUCTION

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 LIB003-010. 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 Objectives

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

2.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the longer term tolerability and safety of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the stability of LDL-C-lowering with LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the pharmacodynamic (PD) effect on serum unbound (free) proprotein convertase subtilisin/kexin type 9 (PCSK9) concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects on serum lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non–HDL-C, very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TG) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the effects on apolipoprotein (apo) B and lipoprotein (a) (Lp[a]) serum concentrations of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo during the Phase 2 double-blind study;
- To assess the pharmacokinetics of LIB003 and PCSK9 following multiple doses of LIB003 300 mg SC Q4W; and
- To assess the frequency of anti-drug (anti-LIB003) antibodies (ADAs) (immunogenicity) of LIB003 300 mg Q4W in patients treated for an additional 52 weeks who were previously

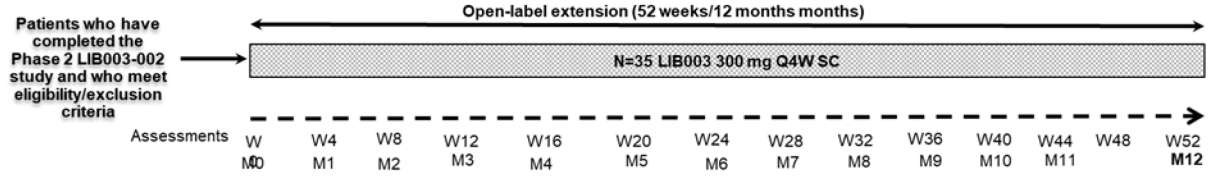
treated with LIB003 at 150 mg, 300 mg, and 350 mg or placebo, including those with detectable ADAs during the Phase 2 double-blind study.

2.2 Study Design

2.2.1 Overview

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

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



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

Patients who have completed the LIB003-002 study and do not meet any exclusion criteria and have completed the informed consent for this extension study will receive LIB003 at a dose of 300 mg Q4W by SC injection at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. In addition to a basic lipid profile, LDL-C will be measured by preparative ultracentrifugation at specified visits during the study. All lipid measurements on Week 0/Month 0 onward will be available to the Investigator, patients, and all site and Sponsor personnel involved in the study. Final safety assessments will include adverse events and the results from physical examinations, electrocardiograms (ECGs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), and immunogenicity testing. Injection site reactions will be assessed at each visit.

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

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

In the case of positive NAbs at the final visit (Week 52/Early Termination), patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months.

Table 1 presents the schedule of procedures of the study.

Table 1. Schedule of Procedures

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

See footnotes on next page.

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

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

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

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

2.2.2 Randomization and Blinding

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

2.2.3 Sample Size Determination

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

2.3 Study Endpoints

2.3.1 Efficacy Endpoints

Two baselines are considered for this study: main study baseline and extension study baseline. Main study baseline is defined as Day 1 of the original Phase 2 dose-finding trial, LIB003-002 study. Extension study baseline is defined as Week 0 of this open-label extension study.

The primary efficacy endpoint is the percent change from main study baseline, in LDL-C level at Week 52 (both calculated by Friedewald formula) of this extension study.

The percent change from main study baseline in LIB003-002 study in LDL-C level at Weeks 24, 36 and 52 (by Friedewald and Hopkins formula and ultracentrifugation/BQuant).

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

2.3.2 Pharmacodynamic Endpoints

Total and unbound (free) serum PCSK9 concentrations at Week 24 and 36 and 52/Early Termination will be assessed.

2.3.3 Pharmacokinetic Endpoints

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

2.3.4 Safety Endpoints

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

2.3.4.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. AEs will be monitored throughout the study and will be coded using Medical Dictionary for Regulatory Activities (MedDRA, v21.0). The severity of all AEs should be graded using the following categories: mild, moderate and severe.

2.3.4.2 Safety Laboratory Evaluations

Clinical laboratory panels for hematology, serum chemistry, and urinalysis will be evaluated from samples collected after ≥10 hours of fasting (ad libitum water is allowed and encouraged) and prior to administration of LIB003 at the time points specified in Table 1.

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

2.3.4.3 Immunogenicity

Patients will be assessed for ADAs at designated study visits specified in Table 1. Patients testing positive for LIB003 antibodies will be tested for NAbs and titer, and may be further characterized for isotype, binding site, affinity, and presence of immune complexes.

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

In the case of positive NAbs at the final visit (Week 52/Early Termination) patients will be asked to return for follow-up testing every 3 months until either NAbs are no longer detectable or the patient has been followed for a period of at least 12 months.

2.3.4.4 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be assessed at designated study visits specified in Table 1. Blood pressure and heart rate will be measured after the patient has been seated or supine for ≥5 minutes.

2.3.4.5 Electrocardiograms

Twelve-lead (single) ECGs will be assessed at designated study visits specified in Table 1. Patients should be resting in the supine position for ≥10 minutes prior to each 12-lead ECG.

2.3.4.6 Physical Examinations

A full physical examination will be performed at the time points specified in Table 1. Injection site reactions will be monitored by examination of injection site at the time points specified in Table 1.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Definition of Baseline

Two baselines are considered: main study baseline and extension study baseline. Main study baseline is defined as Day 1 of the original Phase 2 dose-finding trial, LIB003-002 study. Extension study baseline is defined as Week 0 of this open-label extension study.

3.1.2 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, minimum, and maximum.

3.1.3 Handling of Dropouts and Missing Data

No imputation will be performed for the missing data. Only observed values will be used in data analyses and presentations.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population is defined as all patients who entered the open-label extension study and take at least one dose of study medication.

3.2.2 Safety Population

The Safety Population is defined as all patients who received at least 1 dose of study drug during the open-label extension study. This population will be used to summarize all safety data.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

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

- 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 in total.

Subject disposition data will be presented in a data listing.

3.3.2 Protocol Deviations

Protocol deviations as defined in the Medpace Protocol Deviation Plan will be summarized for the ITT Population. The number and percentage of subjects meeting any criteria will be summarized for each criterion and overall in total. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary.

A data listing will be provided by subject.

3.3.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the Safety Population in total. Categorical demographic variables (e.g., gender, race, and ethnicity) will be summarized using frequency counts and percentages. Continuous variables (e.g., age at informed consent, baseline weight, height, body mass index [BMI], LDL-C level calculated by Friedewald,

Hopkins formula and preparative ultracentrifugation/BQuant), TC, HDL-C, non-HDL-C, VLDL-C, TG, apo B and Lp(a) of this open-label extension study will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum).

3.3.4 Medical History

Medical history will be collected at the screening visit. The reported medical history terms will be coded using MedDRA (Version 21.0). Medical history will be summarized for the Safety Population in total by MedDRA system organ class and preferred term.

Listings of all reported medical history will be provided.

3.3.5 Concomitant Medications

Concomitant medications are defined as medications taken any time after the first dose of study drug of the open-label extension study. Concomitant medications will be coded using the World Health Organization Drug Dictionary B3, Sept 2018 version. Concomitant medications will be summarized with the number and percentages by Anatomical Therapeutic Chemical (ATC) class and preferred term in total for the Safety Population.

Listings will be presented including the ATC, preferred term and verbatim text. The listings will be sorted by subject, chronological start date, therapeutic class, preferred term and verbatim text.

3.3.6 Study Compliance

The number of SC injections for each subject will be summarized with counts and percentages in total.

Listings of all study drug administration will be provided.

3.4 Efficacy Assessment

The efficacy endpoints analysis will be performed based on the ITT Population.

Main study baseline is defined as Day 1 of the Phase 2 dose-finding trial. Baseline values of the Phase 2 (LIB003-002) study (main study), as well as the actual change and percent change from baseline in LDL-C level (by Friedewald and Hopkins formula and ultracentrifugation/BQuant), TC, HDL-C, non-HDL-C, TG, apo B, and Lp(a) will be summarized with descriptive statistics at each visit in total.

Extension study baseline is defined as Week 0 of this open-label extension study. Baseline values of Week 0 in this study (extension study), as well as the actual change and percent change from baseline in LDL-C level (by Friedewald and Hopkins formula and ultracentrifugation/BQuant), TC, HDL-C, non-HDL-C, TG, apo B, and Lp(a) will be summarized with descriptive statistics at each visit in total.

Waterfall plots of percent change from baseline to Weeks 24, 36, and 52 in LDL-C, TC, HDL-C, non-HDL-C, TG, apo B, and Lp(a) will be provided.

3.5 Pharmacodynamic Assessment

The pharmacodynamic endpoints analysis will be performed based on the ITT Population.

Total and unbound (free) serum PCSK9 concentrations at Weeks 24 and 36 and 52 will be summarized descriptively. Change and percent change from both baselines in the Phase 2 (LIB003-002) study and Week 0 in this open-label extension study will be summarized with descriptive statistics at each visit in total.

3.6 Pharmacokinetic (PK) Assessment

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

3.7 Safety Assessment

Safety data will be summarized in total based on the Safety Population.

3.7.1 Adverse Events (AEs)

Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug for this open-label extension study.

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 treatment-emergent serious AEs (TE-SAEs)
- Any study drug related TE-SAEs
- Any TEAEs leading to discontinuation of study
- Any drug related TEAEs leading to discontinuation of study
- Any TEAEs leading to death

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 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.

Listings will be presented specifically for SAEs, TEAEs leading to discontinuation of study, and TEAEs leading to death. All adverse events will be listed.

3.7.2 Clinical Laboratory Tests

Summary statistics will be provided for safety laboratory tests at baseline of this open-label extension study and each scheduled post-baseline visit for hematology, serum chemistry, and urinalysis assessments in total for the Safety Population.

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

Shifts from baseline to worst post-baseline value will be presented for specified lab tests (Alanine aminotransferase [ALT], Aspartate aminotransferase [AST], creatine kinase [CK], total bilirubin) in total. Results will be categorized based on the criteria in the table below.

Parameter	**Categories**			
ALT	Normal	>1xULN to ≤2xULN	>2xULN to ≤3xULN	>3xULN
AST	Normal	>1xULN to ≤2xULN	>2xULN to ≤3xULN	>3xULN
CK	Normal	>1xULN to ≤5xULN	>5xULN to ≤10xULN	>10xULN
Total Bilirubin	Normal	>1xULN to ≤1.5xULN	>1.5xULN to ≤2xULN	>2xULN

The number and percentage of subjects who meet ALT or AST >3xULN and total bilirubin >2xULN 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.

3.7.3 Immunogenicity

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

3.7.4 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 in total. The changes from baseline of this open-label extension study will also be presented.

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

3.7.5 ECG Parameters

ECG parameters (heart rate, PR, QRS, QT, QTcF, and RR) will be summarized using descriptive statistics at baseline and Week 52/ET for the Safety Population in total. The changes from baseline of this open-label extension study will also be presented. The overall interpretation will be summarized by counts and percentages in total.

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

3.7.6 Physical Examinations

Each pre-specified assessment and overall assessment of physical examinations will be summarized by counts and percentages in total.

Physical examination findings will be listed.

3.7.7 Injection Site Reaction Analysis

The number and percentage of subjects with injection site reactions will be summarized by reaction type (pain, tenderness, erythema, swelling, induration, bruising, and itching) by visit and timepoint (pre-dose and 15 minute post-dose) in total. Erythema diameter, swelling diameter, and induration diameter will be summarized with descriptive statistics by visit and timepoint in total.

Injection site assessment data will also be listed.

3.8 Additional Analysis

A sensitivity analysis at Weeks 24, 36 and 52 will be performed on only those subjects who are within the <+3 day visit window (< Day 31) of their last dose.

Additional summary may be considered as needed by combining main study efficacy and/or safety of LIB003 treatment groups with this extension study.

3.9 Interim Analysis

No interim analysis is planned for this study.

Two stage analysis of the efficacy endpoints will be carried out at Weeks 24 and 36 when all the subjects complete Week 24 and 36 visits.

4 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

No changes have been issued or planned.

5 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.3 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.