STATISTICAL ANALYSIS PLAN

CLBS16

An Open-Label Exploratory Clinical Study to Evaluate the Safety and Potential Bioactivity of CLBS16 in Patients with Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease

ClinicalTrials.gov Identifier: NCT03508609

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Version: 1.0

Version Date: 25 May 2020

Replaces Version: not applicable

STATISTICAL ANALYSIS PLAN APPROVAL FORM

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACT	Active clotting time
AE	Adverse events
BMI	Body mass index
CCS	Canadian Cardiovascular Society
CFR	Coronary flow reserve
CLBS16	Autologous CD34+ cells
CMD	Coronary microvascular dysfunction
CRT	Coronary reactivity testing
ECG	Electrocardiography
[redacted]	[redacted]
hsCRP	High sensitivity C-reactive protein
ITT	Intent-to-treat
KDR	Kinase insert Domain Receptor
LpPLa2	Lipoprotein-associated phospholipase A2
[redacted]	[redacted]
MedDRA	Medical Dictionary of Regulatory Activities
[redacted]	[redacted]
PAT	Peripheral arterial tonometry
QWISE	Study of Quinapril in Women with Chest Pain, Coronary Flow Reserve Limitations and Evidence of Myocardial Ischemia
SAE	Severe adverse events
[redacted]	[redacted]
SI	System International
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for this phase 2, an Open-Label Exploratory Clinical Study to Evaluate the Safety and Potential Bioactivity of CLBS16 in Patients with Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease.

This analysis plan was developed based on the principles discussed in the International Council on Harmonisation E3 and E9 Guidelines and in reference to protocol CLBS16-P01.

2. OBJECTIVES

2.1. PRIMARY OBJECTIVES

To evaluate the safety and tolerability of intracoronary delivery of CLBS16 in patients with CMD and without obstructive coronary artery disease.

2.2. SECONDARY OBJECTIVES

To evaluate the potential efficacy of CLBS16 by examining the following exploratory parameters:

- Coronary microvascular function as measured by coronary flow reserve
- Peripheral arterial tonometry (PAT)

2.3. STUDY DESIGN

This is a phase 2 open-label clinical study to evaluate the safety, tolerability, and potential bioactivity of CLBS16 in patients with coronary microvascular dysfunction and without obstructive coronary artery disease.

Screening Phase

Patients who provide informed consent will be screened for eligibility within 60 days before beginning the study treatment phase. Patients must be on stable medical therapy for 30 days prior to screening and until treatment with CLBS16.

[redacted]

Treatment Phase

[redacted]

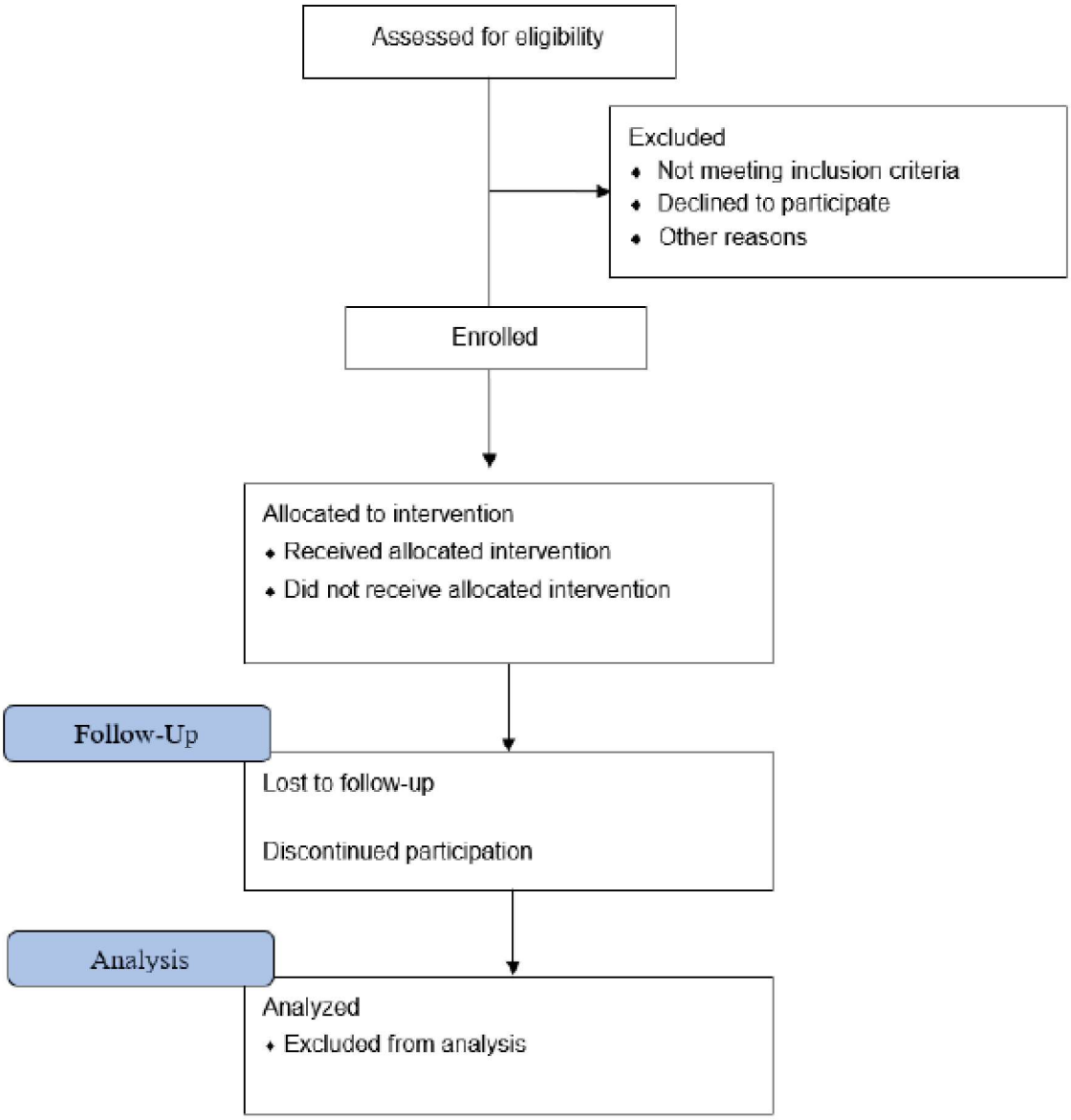
[redacted]

Follow-up Phase

The occurrence of adverse events (AEs), serious adverse events (SAEs) [redacted] will be collected for all subjects during the treatment and 12-month follow-up period to evaluate the safety and tolerability of intracoronary administration of CLBS16. Efficacy assessments will be performed through 6 months to evaluate the potential bioactivity of CLBS16 in patients with coronary microvascular dysfunction.

[redacted]

[redacted]



3. ANALYSIS ENDPOINTS

3.1. SAFETY ENDPOINT

- Adverse events, including serious adverse events
- Laboratory investigations
- Physical examinations
- Vital signs
- Electrocardiographic findings
- [redacted]

3.2. AE OF SPECIAL INTEREST (AESI)

[redacted]

3.3. EFFICACY ENDPOINT(S)

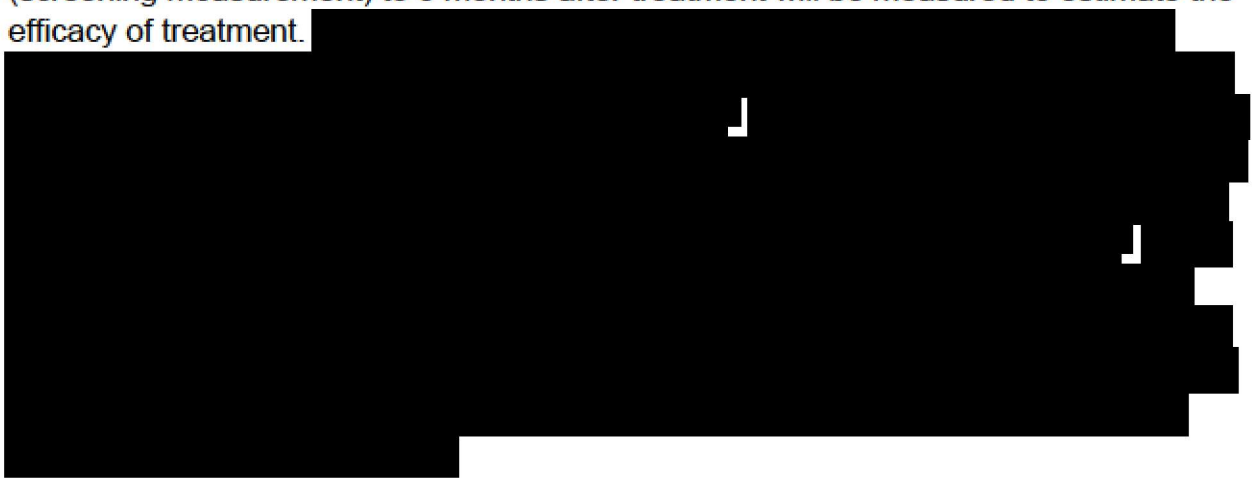
- Change from baseline in peak coronary flow reserve (CFR) to intracoronary adenosine at 6 months
- [redacted]
- Change from baseline in peripheral arterial tonometry measurements as RHI (reactive hyperaemia index) at 6 months
- [redacted]

3.4. EXPLORATORY ENDPOINT(S)

[redacted]

4. DETERMINATION OF SAMPLE SIZE

This is an exploratory study to estimate the effect of CLBS16 treatment in this population of patients. The primary endpoint of the change in CFR from baseline (screening measurement) to 6 months after treatment will be measured to estimate the efficacy of treatment.



5. METHOD OF ANALYSIS AND PRESENTATION

5.1. GENERAL PRINCIPLES

Statistical analysis will be performed using the SAS System, Version 9.4.

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. Continuous data will be summarized using number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

5.1.1. MISSING DATA

[redacted]

5.1.2. DEFINITION OF STUDY DAY AND VISIT WINDOW

Study day will be calculated relative to the date of the dose of [redacted] in the study. The study day prior to the GCSF dosing will be calculated as:

Date of assessment/event – date of [redacted] dosing

The study day on or after the dose of [redacted] will be calculated as:

Date of assessment/event – date of [redacted] dosing + 1.

Baseline is defined as the last non-missing measurement prior to the dosing of [redacted] (Study Day 1). The visit windows for the postbaseline visit are defined in Table 1 and Table 2. If a subject has more than 1 measurement in the same visit window, the measurement closest to the scheduled visit will be used. If 2 measurements in the same window are of equal distance to the scheduled visit, the measurement that occurs after the scheduled visit will be used. If 2 or more measurements occur on the same day, the last value obtained will be used.

Table 1 Visit Analysis Windows for Efficacy

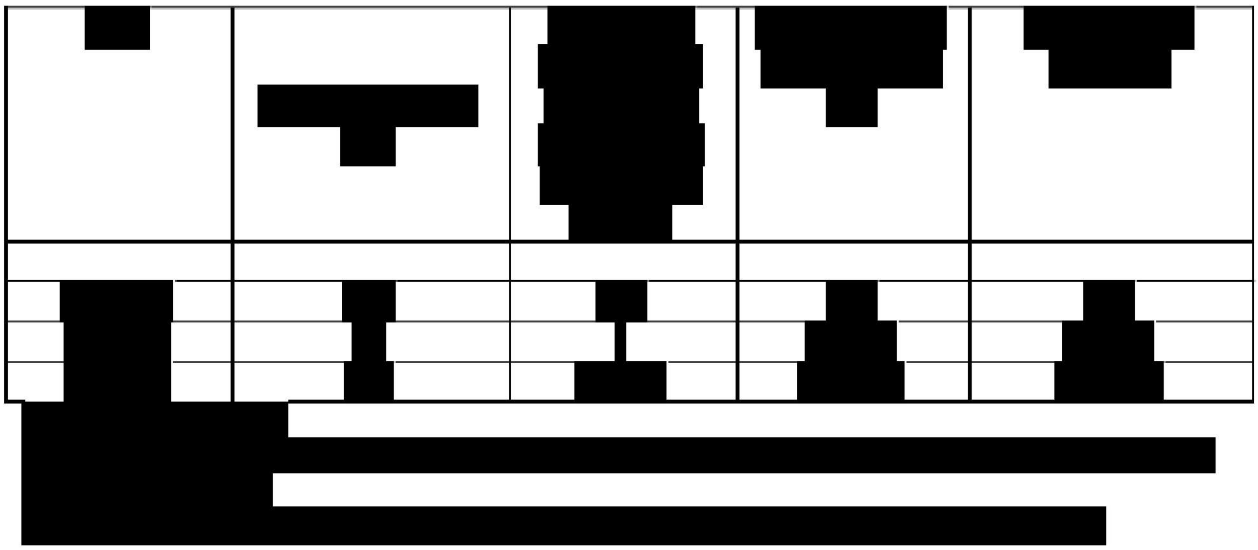


Table 2 Visit Analysis Windows for Safety

Visit	Scheduled Visit Day	Hematology	Chemistry	Vital Sign	ECG	Cardiac Markers
Baseline	1	<=1	<=1	<=1	<=1	<=1
Month 6 After D*	187	136-194	136-194	136-194	D*+2-194	106-194

D*: CD34+ dosing day

Note: [redacted] postdosing have a visit window of ± 4 days. Subsequent visits postdosing have a visit window of ± 14 days.

(a): on CD34+ dosing date, data include 0,2,4,6 hours after dosing.

(b): on CD34+ dosing date, data include 0,2,6 hours after dosing.

5.2. ANALYSIS SET

5.2.1. SAFETY ANALYSIS SET

The safety analysis set will consist of all subjects who have been consented in the study and have received treatment [redacted] The safety analysis set may be further subdivided for subjects who received only a subset of the intended procedures.

5.2.2. FULL ANALYSIS SET

The intent-to-treat analysis (ITT) set will consist of all subjects who received treatment with CLBS16.

5.2.3. PER-PROTOCOL ANALYSIS SET

The per-protocol analysis set will exclude subjects who had deviations that may impact critical efficacy variables.

5.3. DISPOSITION OF SUBJECTS

A subject disposition summary will be provided. Subject's study completion data, including reasons for premature termination, will be provided in listings and summarized.

Major protocol deviations will be summarized.

A summary of screening failures will also be provided.

5.4. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics variables will be summarized for the full analysis set.

For continuous variables (age, weight, height and BMI), summary statistics will be generated. For categorical variables, the number and percentage of subjects in each category will be presented.

5.5. MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

Medical history and concurrent medical conditions will be presented in a data listing and will be summarized.

5.6. MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

All medication history and concomitant medications will be coded by therapeutic classification, subclassification, and medication using the World Health Organization Drug Dictionary (WHODrug). A concomitant medication is defined as a medication that is ongoing as of Study Day 1, ends on or after Study Day 1, or starts on or after Study Day 1 and no more than 1 day after the last dose of study drug.

The number and percentage of subjects taking each concomitant medication will be summarized for the safety analysis set. A subject with 1 or more concomitant medications within the same level of the WHODrug classification will be counted only once in that level. WHODrug preferred term and therapeutic classification will be used for summary:

- Concomitant medications that were ongoing at baseline and those that started after baseline.

5.7. STUDY DRUG EXPOSURE AND COMPLIANCE

Summaries of extent of exposure will include descriptive statistics for [redacted] the actual dose of CLBS16 injected.

[redacted]

5.8. EFFICACY ANALYSIS

5.8.1. PRIMARY EFFICACY ENDPOINT

The primary measurements of CFR will be used to estimate the efficacy of treatment and the overall analysis framework will be paired t tests using baseline and 6-month visit data. [redacted]

5.8.2. ADDITIONAL EFFICACY ENDPOINT

Continuous variables will be analyzed using paired t test using change from baseline data. The change from baseline and confidence intervals will be estimated. [redacted]

[redacted]

5.8.3. EXPLORATORY EFFICACY ENDPOINTS

[redacted]

5.9. SAFETY ANALYSIS

Safety will be monitored and the frequency and proportion of patients experiencing AEs, SAEs [redacted] during the 12-month follow-up period will be reported.

5.9.1. ADVERSE EVENTS

All summary tables will be based on "treatment-emergent" adverse events, defined as any AE with onset on or after the date of [redacted]

AEs will be presented in summary tables. An overview of subjects with AEs and the frequency of AEs will be summarized by seriousness, severity, and relatedness. If the AE is assessed as possibly related or probably related, the investigator will be asked to assess if the AE is related to any of the following:

[redacted]

- Cell delivery

- CLBS16

Tables will be prepared to list each AE by the Medical Dictionary of Regulatory Activities (MedDRA) term, the number of subjects who experienced an AE at least once, and the rate of subjects with AE(s).

Serious and non-serious AEs will be categorized and summarized according to MedDRA terms and presented for each class of severity (severe, moderate, mild). A summary of the number and percent of subjects experiencing AEs in each system organ class and preferred term will be presented along with the subject identifiers.

All AEs for each subject will be listed, giving the MedDRA system organ class, preferred term, severity grade, relation to IP, onset date, stop date, action taken, outcome, date IP was applied, and study day of AE start. This will be prepared for serious and non-serious AEs separately.

5.9.2. CLINICAL LABORATORY EVALUATIONS

Central clinical laboratory results will be used for the safety analysis. For hematology, coagulation parameters, and clinical chemistry parameters, summary statistics and shift tables will be created.

Individual results for clinical hematology, chemistry laboratory tests that are within the predefined clinically significant abnormal laboratory value criteria will be summarized in tables. All clinical laboratory data will be presented in data listings.

Summaries and listings of laboratory data will be presented in conventional units.

5.9.3. VITAL SIGNS

Vital Signs will be summarized in the same way the safety parameters are summarized.

5.9.4. ECGS

ECG intervals, and any clinically meaningful -in the opinion of the investigator-ECG abnormalities will be summarized at each scheduled time point.

[redacted]

5.10. INTERIM ANALYSIS

No interim analysis is planned.

5.11. CHANGES IN THE STATISTICAL ANALYSIS PLAN

6. APPENDIX A SCHEDULE OF ASSESSMENTS

[redacted]

[redacted]

[redacted]

[redacted]

7. REFERENCES

1. Garg R, Rao AD, Baimas-George M, Hurwitz S, Foster C, Shah RV, Jerosch-Herold M, Kwong RY, Di Carli MF and Adler GK. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. *Diabetes*. 2015;64:236-42.
2. Pauly DF, Johnson BD, Anderson RD, Handberg EM, Smith KM, Cooper-DeHoff RM, Sopko G, Sharaf BM, Kelsey SF, Merz CN and Pepine CJ. In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: A double-blind randomized study from the National Heart, Lung and Blood Institute Women's Ischemia Syndrome Evaluation (WISE). *American heart journal*. 2011;162:678-84.