CLINICAL STUDY PROTOCOL

CLBS16 (formerly CLBS14)

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

PROTOCOL NUMBER: CLBS16-P01 (formerly CLBS14-P01)

ClinicalTrials.gov Identifier: NCT03508609

Version Number: 7

Version Date: 26 August 2019

Study Sponsor(s): Caladrius Biosciences
110 Allen Road, Second Floor
Basking Ridge, NJ 07920

PROTOCOL APPROVAL FORM

CLINICAL STUDY PROTOCOL

CLBS16-P01

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

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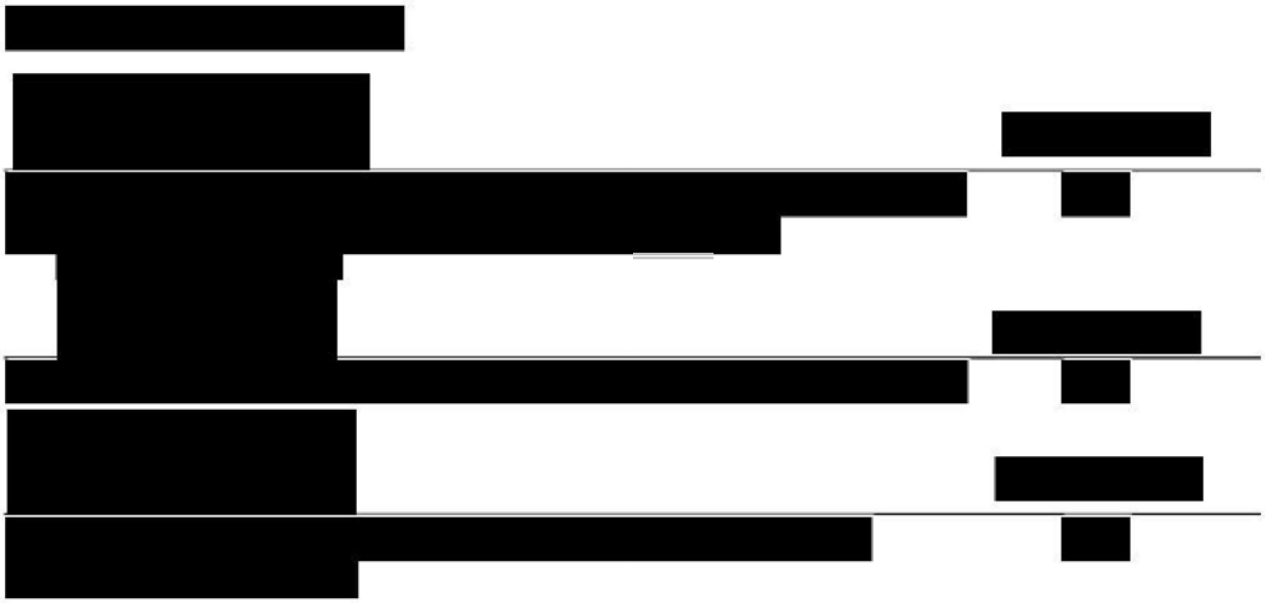


1. PERSONNEL AND FACILITIES

Sponsor Caladrius Biosciences, Inc. 110 Allen Road, Second Floor Basking Ridge, NJ 07920 Main: (908) 842-0100	**Contact for Reporting Serious Adverse Events** [redacted]
Medical Monitor [redacted]	
Study Manager (Primary Study Contact) [redacted]	

Note: Changes to Personnel and Facilities do not constitute an amendment and will be updated as needed.

2. STUDY SYNOPSIS

INVESTIGATIONAL PRODUCT	
Name of Investigational Product	CLBS16
Name(s) of Active Ingredient(s)	Granulocyte-Colony Stimulating Factor (G-CSF) mobilized peripheral blood derived autologous CD34+ cells
CLINICAL CONDITION(S)/INDICATION(S)	
• Coronary Microvascular Dysfunction	
PROTOCOL ID	CLBS16-P01
PROTOCOL TITLE	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
Short Title	Exploratory study of CLBS16 for Coronary Microvascular Dysfunction
STUDY PHASE	2
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
• To evaluate the bioactivity of intracoronary delivery of autologous CD34+ cells (CLBS16) in patients with coronary microvascular dysfunction (CMD) and without obstructive coronary artery disease, [redacted]	
Primary Objective	
• To evaluate the safety and tolerability of intracoronary delivery of CLBS16 in patients with CMD and without obstructive coronary artery disease.	
Secondary Objective(s)	
To evaluate the potential efficacy of CLBS16 by examining the following exploratory parameters: • Coronary microvascular function as measured by coronary flow reserve [redacted] • Peripheral arterial tonometry (PAT) [redacted]	

STUDY DESIGN	
Study Type	Interventional
Control Type	None
Study Classification	Safety/Efficacy
Blinding Schema	Open-label
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] [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]
Planned Duration of Subject Participation	13 months
Endpoints	
Safety Endpoints • Adverse events, including serious adverse events • Laboratory investigations • Physical examinations	

- Vital signs
- Electrocardiographic findings

[redacted]

Efficacy Endpoints

- Change from baseline in coronary flow reserve at 6 months

[redacted]

- Change from baseline in peripheral arterial tonometry measurements at 6 months

[redacted]

INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Investigational Product(s)	**Dosage form**: Solution/Suspension **Dosage frequency**: Once [redacted]
Mode of Administration	Cell infusion into a coronary artery will be performed in the cardiac catheterization laboratory.
SUBJECT SELECTION	
Planned # of Subjects	Approximately 20
Population to be Studied	Men and women over 18 years of age without obstructive disease on coronary angiogram within 6 months prior to screening [redacted]

	[redacted]

Inclusion Criteria

1. Men or women age ≥18
2. History of effort-induced anginal symptoms and currently experiencing angina at least 3 times per week
3. No obstructive disease [redacted]
4. If subject is of childbearing potential, presents with a negative pregnancy test, and agrees to employ adequate birth control measures for the duration of the study. [redacted]
5. Subject is willing and able to comply with the requirements of the protocol
6. Stable medical therapy for 30 days prior to screening [redacted]
7. Able to provide signed informed consent

Exclusion Criteria

1. Myocardial infarction within 90 days [redacted]
2. Prior evidence of obstructive heart disease including history of Percutaneous Coronary Intervention (PCI) and/or Coronary Artery Bypass Grafting (CABG)
3. Planned percutaneous coronary intervention or CABG
4. Diagnosis of other specific cardiac disease [redacted]

7. Subject currently uses coumadin, [redacted] or plans to use one of these agents during the time frame of the trial [redacted]
11. Subject tests positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C
12. Subject has active inflammatory disease or autoimmune disease, or is in a chronic immunosuppressive state
13. Recent history of abuse or current abuser of recreational drugs [redacted]
14. Subject is pregnant or lactating [redacted]
15. Malignant neoplasm [redacted] within 5 years prior to screening
16. Subject has participated in another clinical study within 90 days [redacted]
17. History of sickle cell disease [redacted]

STATISTICAL ELEMENTS

Power Estimate

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

[redacted]

Planned Statistical Analysis

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 (screening value) and 6-month visit data. [redacted]

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin converting enzyme
ACT	Active clotting time
AE	Adverse events
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AP	Anterior-posterior
APTT	Activated partial thromboplastin time
APV	Average peak velocity
ASA	Acetyl salicylic acid (aspirin)
AST	Aspartate aminotransferase
[redacted]	[redacted]
BMI	Body mass index
BUN	Blood urea nitrogen
BW	Body weight
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CBC	Complete blood count
cc	Cubic centimeter
CCS	Canadian Cardiovascular Society
CFR	Coronary flow reserve
CFR	Code of federal regulations
CK	Creatine kinase
CLBS16	Autologous CD34+ cells
CMD	Coronary microvascular dysfunction
cMRI	Cardiac magnetic resonance imaging
CMV-IgM	Cytomegalovirus immunoglobin M
CRP	C-reactive protein
CRT	Coronary reactivity testing
DCM	Dilated cardiomyopathy
ECG	Electrocardiography
EDMF	Endothelial-dependent microvascular function
e-GFR	Estimated glomerular filtration rate
EIMF	Endothelial-independent microvascular function
EPC	Endothelial progenitor cells
FDA	Food and Drug Administration
FS	Fractional shortening

Abbreviation	Definition
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular filtration rate
HBc antibody	Hepatitis C surface antigen
HBs antigen	Hepatitis B surface antigen
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
[redacted]	[redacted]
hsCRP	High sensitivity C-reactive protein
HTLV-1	Human T-lymphotrophic virus-1
ICH	International Council on Harmonisation
IHD	Ischemic heart disease
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technologies
ITT	Intent-to-treat
KDR	Kinase insert Domain Receptor
LAD	Left anterior descending
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LpPLa2	Lipoprotein-associated phospholipase A2
LV	Left ventricular
LVEF	Left ventricular ejection fraction
[redacted]	[redacted]
MESA	Multi-Ethnic Study of Atherosclerosis
mKCCQ	Modified Kansas City Cardiomyopathy Questionnaire
MNC	Mononuclear cells
NTG	Nitroglycerin
NT-proBNP	N-terminal pro B-type natriuretic peptide
Parvovirus B19-IgM	Parvovirus B19-IgM
PAT	Peripheral arterial tonometry
[redacted]	[redacted]
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PT	Prothrombin time

Abbreviation	Definition
QWISE	Study of Quinapril in Women with Chest Pain, Coronary Flow Reserve Limitations and Evidence of Myocardial Ischemia
RAO	Right anterior oblique
SAE	Severe adverse events
[redacted]	[redacted]
[redacted]	[redacted]
SIC	Subject identification code
T-bil	Total bilirubin
TBV	Total blood volume
T-cho	Total cholesterol
TG	Triglyceride
TOPCARE-AMI	Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction
T-pro	Total protein
VTBI	Volume to be injected
WISE	Women's Ischemia Syndrome Evaluation

4. TABLE OF CONTENTS

5. SCHEDULE OF ASSESSMENTS

[redacted]

[redacted]

[redacted]

6. BACKGROUND AND SIGNIFICANCE

6.1 Coronary Microvascular Dysfunction

Patients with symptoms, evidence of ischemia, and no obstructive coronary artery disease (CAD) are prevalent and increasing in frequency.[3] The prevalence of nonobstructive CAD at coronary angiography amongst patients presenting with chest pain is 20% to 30%[4, 5] and has been reported to be up to 50%.[6] Such patients have disability, healthcare resource consumption, and costs similar to those with obstructive CAD.[7, 8] Functional coronary microvascular abnormalities mediate ischemia and cause angina[9, 10] and have been linked to adverse clinical outcomes.[11, 12] Thus, coronary microvascular dysfunction (CMD) may serve as the underlying mechanism for the symptoms and cardiovascular events observed in patients with nonobstructive ischemic heart disease (IHD).

In a recent study of patients with chest pain and nonobstructive CAD (N=1,439) who underwent a comprehensive and invasive assessment of coronary microvascular function, more than two-thirds of patients had some sort of coronary microvascular dysfunction.[13] Considerable data document that CMD contributes to myocardial perfusion abnormalities in regions supplied by vessels without epicardial stenosis[14, 15, 16] in patients with risk factors and/or angina, but without epicardial stenosis.[17, 18, 19, 20] It is now evident that CMD is not benign and is predictive of adverse cardiovascular outcomes. In the MESA (Multi-Ethnic Study of Atherosclerosis), both myocardial flow (cardiac magnetic resonance imaging [cMRI]) during adenosine-induced hyperemia and flow reserve were inversely associated with risk factor burden.[21] CMD has been documented among symptomatic women without flow-limiting coronary stenosis in the Women's Ischemia Syndrome Evaluation (WISE)[22, 23] by directly measured (Doppler flow wire) coronary flow, by cMRI,[24] and by positron emission tomography (PET).[11] These studies have linked CMD and atherosclerosis risk factors with adverse outcomes over follow-up. CMD has also been replicated in another female cohort,[25] providing additional support for its link with several risk factors.

6.2 CD34+ Cell Therapy

The potential role of autologous CD34+ cells for the treatment of CMD is supported by findings from the Doppler Substudy of the REPAIR-AMI trial, which demonstrated that coronary microvascular function improved with administration of progenitor cells in patients with reperfused acute myocardial infarction. Intracoronary infusion of bone marrow cells (BMCs; rich in CD34+ cells) in patients with reperfused AMI was associated with a normalization of CFR in the infarct-related artery within 4 months and hence a profound improvement in maximal vascular conductance capacity. Therefore,

these data support the hypothesis that BMCs infused into the coronary circulation reconstitute damaged endothelium and promote neovascularization in the area of the infarct vessel in patients with acute myocardial infarction (AMI).[26] These results are supported by the Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial, which was not placebo controlled and suggested that intracoronary transplantation of progenitor cells effectively improves CFR in the infarct-related artery in patients with successfully reperfused AMI.[27]

Intracoronary cell delivery may be applicable to patients with CMD. The efficacy of cell delivery in treatment of cardiovascular disease is gaining interest, and cell therapy with CD34+ cells has been shown to be safe and feasible. While cell therapy has been explored in treatment of late stage coronary atherosclerosis such as acute myocardial infarction, no study to date has evaluated the role of cell therapy in patients with early coronary atherosclerosis, non-obstructive coronary arteries, and CMD.

6.3 Findings from Nonclinical Studies

6.3.1 Therapeutic Potential of Ex Vivo Expanded Endothelial Progenitor Cells in Myocardial Ischemia in Rats

In a study conducted by Kawamoto *et. al.*, the researchers examined the therapeutic potential and safety of endothelial progenitor cells (EPCs) in an animal model of myocardial ischemia.[28] Peripheral blood MNCs obtained from healthy human adults were cultured to promote the growth of EPCs and injected intravenously (IV) into rat models of myocardial ischemia. Five rats were injected with 1 x 10^6 EPCs 3 hours after ischemia induction (EPC group) and the control group (5 rats) received culture media alone.

Echocardiography, performed at baseline and 28 days after ischemia, revealed ventricular dimensions that were significantly smaller and fractional shortening that was significantly greater in the EPC vs. control group by Day 28. Regional wall motion was better preserved in the EPC vs. control group. Following sacrifice on Day 28, necropsy examination revealed that capillary density was significantly greater in the EPC group than in the control group. Additionally, the extent of left ventricular (LV) scarring was significantly less in rats receiving EPCs compared to the controls. Immunohistochemistry revealed capillaries that were positive for human-specific EPCs.

The conclusion from the study was that *ex vivo* expanded progenitor cells can incorporate into foci of myocardial neovascularization and have a favorable impact on preservation of LV function.

6.3.2 Human CD34+ Cell Therapy in Rat Model of Myocardial Ischemia

A safety and efficacy study was performed with human CD34+ cells in the athymic nude rat model of myocardial ischemia.* Mononuclear cells (MNCs) were collected by apheresis from a healthy human volunteer who underwent mobilization (10 µg/kg G-CSF subcutaneously) 3 days prior to MNC collection. CD34+ cells were isolated and injected into rat models of myocardial ischemia via intramyocardial injection. Animals were assigned to one of 6 treatment groups: phosphate buffered saline (PBS); 5×10^3 CD34+ cells/kg; 5×10^5 CD34+ cells/kg; 2×10^7 CD34+ cells/kg; 5×10^5 unselected MNC; or a high dose unselected MNC group that contained 5×10^5 unselected CD34+ cells.

Analysis of the efficacy data revealed a statistically significant improvement in both fractional shortening (29.5±1.6% vs. 23.23±2.5%, $p<0.05$) and regional wall motion score (22.5±0.6 vs. 24.4±0.7, $p<0.05$) in animals treated with 5×10^5 CD34+ cells/kg when compared to animals in the PBS group, respectively. A statistically significant improvement was also noted in fractional shortening (FS) (28.8±1.8% vs. 23.23±2.5%, $p<0.05$) in animals treated with the high dose of unselected MNC containing 5×10^5 unselected CD34+ cells when compared to animals treated with PBS.

Moreover, in all animals studied for 28 days, the percent of fibrosis was calculated by morphometric analysis of 4 representative elastic tissue trichrome stained sections for each animal. The percent fibrosis/entire left ventricular area was significantly lower in animals treated with 5×10^5 CD34+ cells/kg when compared to animals treated in any other group (15.9±1.5% vs. 23.7±1.4% PBS group, 23.8±2.7 low dose CD34+ group, 27.2±2.4% low dose MNC group, and 22.7±3.1 high dose MNC group, $p<0.03$).

The pre-clinical studies above show that EPCs and CD34+ cells are safe and efficacious for myocardial ischemia treatment in the rat model.

6.4 Findings from Clinical Studies

6.4.1 Intramyocardial Autologous CD34+ Cell Therapy for Refractory Angina (ACT34-CMI)

Losordo et al. conducted a prospective, double-blind, randomized, phase 2 study (NCT00300053) in 167 patients with no-option refractory angina evaluating 2 doses (1×10^5 or 5×10^5 cells/kg) of mobilized autologous CD34+ cells compared with an equal volume of diluent (placebo).[29] Treatment was distributed into 10 sites of ischemic, viable

* Data on file; BB-IND 11196 Pharmacology and Toxicology Section C.

myocardium with a NOGA™ mapping injection catheter. The primary outcome measure was weekly angina frequency 6 months after treatment. Weekly angina frequency was significantly lower in the low-dose group than in placebo-treated patients at both 6 months (6.8±1.1 versus 10.9±1.2, P=0.020) and 12 months (6.3±1.2 versus 11.0±1.2, P=0.035); measurements in the high-dose group were also lower, but not significantly. Similarly, improvement in exercise tolerance was significantly greater in low-dose patients than in placebo-treated patients (6 months: 139±151 versus 69±122 seconds, P=0.014; 12 months: 140±171 versus 58±146 seconds, P=0.017) and greater, but not significantly, in the high-dose group. During cell mobilization and collection, 4.6% of patients had cardiac enzyme elevations consistent with non-ST segment elevation myocardial infarction. Mortality at 12 months was 5.4% in the placebo-treatment group with no deaths among cell-treated patients. These results provide evidence for the potential bioactivity of autologous CD34+ cells in myocardial ischemia as well as demonstrating the feasibility of this treatment strategy in a multi-center study.

6.4.2 Autologous CD34+ Cell Therapy for Heart Failure

Vrtovec et al. have performed a prospective, randomized clinical study (NCT01350310) investigating long-term effects of CD34+ stem cell therapy in patients with nonischemic dilated cardiomyopathy (DCM).[30] Of 110 patients with DCM, 55 were randomized to CD34+ cell transplantation (SC group) and 55 patients did not receive stem cell therapy (Controls). In the SC group, peripheral blood CD34+ cells were mobilized by granulocyte-colony stimulating factor and collected via apheresis. Patients underwent myocardial scintigraphy, and CD34+ cells were injected in the coronary artery supplying the segments with reduced viability. At 5 years, stem cell therapy was associated with an increase in LVEF (from 24.3 ± 6.5% to 30.0 ± 5.1%; P = 0.02), an increase in 6-minute walk distance (from 344 ± 90 m to 477 ± 130 m; P <0.001), and a decrease in N-terminal pro B-type natriuretic peptide (NT-proBNP) (from 2322 ± 1234 pg/mL to 1011 ± 893 pg/mL; P <0.01). During follow-up, 27 (25%) patients died, and 9 (8%) underwent heart transplantation. Of the 27 deaths, 13 were attributed to pump failure and 14 to sudden cardiac death. Total mortality was lower in patients receiving SC therapy (8/55, 14%) than in Controls (19/55, 35%) (P = 0.01). The same was true of the pump failure (3/55 vs. 10/55, P = 0.03) but not of the sudden cardiac death (5/55 vs. 9/55, P = 0.39). Thus, it appears that intracoronary stem cell transplantation is associated with improved ventricular remodeling, better exercise tolerance, and improved long-term survival in patients with chronic heart failure due to nonischemic dilated cardiomyopathy.

In addition, Poglagen, et al. investigated the clinical effects of intramyocardial transplantation of selected CD34+ stem cells in patients with ischemic cardiomyopathy in a prospective Phase 1 crossover study (NCT01350310).[31] A total of 33 patients with

ischemic cardiomyopathy and New York Heart Association class III and left ventricular ejection fraction <40% were enrolled. In phase 1, patients were treated with medical therapy for 6 months. Thereafter, all patients underwent intramyocardial CD34+ cell transplantation. Peripheral blood CD34+ cells were mobilized by granulocyte colony stimulating factor, collected via apheresis, and injected intramyocardially in the areas of hibernating myocardium. Patients were followed up for 6 months after the procedure (phase 2). Two patients died during phase 1 and none during phase 2. The remaining 31 patients were 85% men, aged 57±6 years. In phase 1, we found no change in left ventricular ejection fraction (from 25.2±6.2% to 27.1±6.6%; P=0.23), NT-proBNP (from 3322±3411 to 3672±5165 pg/mL; P=0.75) or 6-minute walk distance (from 373±68 to 411±116 m; P=0.17). In contrast, in phase 2 there was an improvement in left ventricular ejection fraction (from 27.1±6.6% to 34.9±10.9%; P=0.001), increase in 6-minute walk distance (from 411±116 to 496±113 m; P=0.001), and a decrease in NT-proBNP (from 3672±5165 to 1488±1847 pg/mL; P=0.04). The average number of injected CD34+ cells was $90.6\pm7.5\times10^6$. Higher doses of CD34+ cells and a more diffuse distribution of intramyocardial cell injections were associated with better clinical response. These findings suggest that intramyocardial CD34+ cell transplantation may be associated with improved left ventricular function, decreased NT-proBNP levels, and better exercise capacity in patients with ischemic cardiomyopathy.

6.5 Description of Investigational Product

[redacted]

7. STUDY OBJECTIVES

7.1 Primary Objective

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

7.2 Secondary Objectives

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

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

[redacted]

8. 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 no obstructive coronary artery disease. The study will be conducted in the phases as outlined below:

8.1 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]

8.2 Treatment Phase

[redacted]

[redacted]

[redacted]

8.3 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]

8.4 Duration of Subject Participation

All subjects will be followed for 12 months following intracoronary administration of CLBS16.

8.5 Randomization and Blinding

This is an open-label study with a single group receiving intracoronary CLBS16 infusion, therefore randomization and blinding do not apply to this clinical study.

8.6 Stopping Rules

8.6.1 Stopping for Individual Patients

Treatment of an individual patient should not be undertaken if any issue is identified which would create an unreasonable risk for intracoronary administration of CLBS16. Treatment should also not be undertaken if any issue is identified which would create an unreasonable risk for coronary microvascular testing. Any such decision may be made prior to initiation of the treatment procedure or at any point during a microvascular

testing or intracoronary administration procedure. Patients not treated with CLBS16 may be replaced at the discretion of the Sponsor. [redacted]

8.6.2 Stopping of the Study

The investigators and the medical monitor for this study will review adverse events on an ongoing basis and will communicate with each other if any evolving safety signal is perceived. In the event that an evolving safety signal is perceived, the medical monitor may choose to discontinue treatment of further patients. However, observation of patients already treated should continue to the extent possible.

9. STUDY ENDPOINTS

9.1 Safety Endpoints

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

[redacted]

9.2 Efficacy Endpoints

- Change from baseline in coronary flow reserve at 6 months

[redacted]

- Change from baseline in peripheral arterial tonometry measurements at 6 months

[redacted]

[redacted]

9.3 [redacted]

[redacted]

10. STUDY POPULATION

Men and women 18 years of age and over, without obstructive disease [redacted]

10.1 Inclusion Criteria

Subjects who meet **ALL** of the following criteria are eligible for this study:

1. Men or women age ≥18
2. History of effort-induced anginal symptoms and currently experiencing angina at least 3 times per week.

3. No obstructive disease [redacted]
4. If subject is of childbearing potential, presents with a negative pregnancy test, and agrees to employ adequate birth control measures for the duration of the study. [redacted]
5. Subject is willing and able to comply with the requirements of the protocol
6. Stable medical therapy for 30 days prior to screening [redacted]
7. Able to provide signed informed consent

10.2 Exclusion Criteria

1. Myocardial infarction within 90 days [redacted]
2. Prior evidence of obstructive heart disease including history of Percutaneous Coronary Intervention (PCI) and/or Coronary Artery Bypass Grafting (CABG)
3. Planned percutaneous coronary intervention or CABG
4. Diagnosis of other specific cardiac disease [redacted]
7. Subject currently uses coumadin, [redacted] or plans to use one of these agents during the time frame of the trial [redacted]

[redacted]

11. Subject tests positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C
12. Subject has active inflammatory disease or autoimmune disease, or is in a chronic immunosuppressive state
13. Recent history of abuse or current abuser of recreational drugs [redacted]
14. Subject is pregnant or lactating [redacted]
15. Malignant neoplasm [redacted] within 5 years prior to screening
16. Subject has participated in another clinical study within 90 days [redacted]
17. History of sickle cell disease [redacted]

11. INVESTIGATIONAL PRODUCT

The process for obtaining autologous CD34+ cells is as follows:

[redacted]

11.1 [redacted]

[redacted]

11.2 [redacted]

[redacted]

11.3 Description of Treatment

[redacted]

The dose level was selected based on results from previous clinical studies, which were able to demonstrate efficacy from intracoronary administration of CD34+ cells. Three studies provide support for the dose level in this study. The first is a study by Leziac, et al. in which it was demonstrated that treatment with CD34+ cells led to improved myocardial perfusion in patients with nonischemic dilated cardiomyopathy.[34] In that study, the maximum dose that could be manufactured was administered, with a range between 54 x 10^6 cells and 284 x 10^6 cells. All doses were well tolerated. In a second study, Wang, et al. examined CD34+ cell therapy in patients with intractable angina.[35] In their study, the mean number of CD34+ cells infused was also limited by the number of cells available from the manufacturing procedure and averaged 56 ± 23 x 10^6 cells per patient. In the Wang study, significant improvements were observed in frequency of angina episodes, nitroglycerin use, and other measures. All treatments were well tolerated. The third reference study for cell dose was the study by Vrtovec, et al., in which effects of CD34+ cells were examined in patients with nonischemic dilated cardiomyopathy.[30] In that study, the number of cells infused was also limited by the number of cells available from the manufacturing procedure and averaged 113 ± 26 x 10^6 cells per patient. Significant improvements were seen in left ventricular ejection fraction, 6 minute walk test, and other measures out to 5 years after treatment. All treatments were well tolerated.

Regarding route of administration, many previous studies have used either intramyocardial injection or intracoronary infusion of CD34+ cells. Both routes of administration have been effective at improving cardiac function. However, there has been no clear evidence that one would be more effective than the other, and due to the less invasive nature of intracoronary infusion versus intramyocardial injection, the intracoronary infusion route of administration was selected.

[redacted]

11.4 Investigational Product Accountability

The investigator will ensure that the investigational product (IP) is stored as instructed in the investigational product manual and that the storage area is secured, with access

limited to authorized study personnel. The investigator will maintain records that the IP was received, including the date received, IP lot number, date of manufacture or expiration date, amount received, and disposition. IP must be dispensed only at the institution specified for each study site. Records will be maintained that include the subject's initials and subject identification code (SIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be destroyed in accordance with applicable laws and study site procedures or, if requested, returned to the Sponsor or Sponsor's representative. If IP is to be destroyed, the investigator will provide documentation in accordance with Sponsor's specifications.

11.5 Packaging, Labeling, and Storage

[redacted] A label will include subject identifiers, product expiration date & time, clinical site designator, product volume, product identifier, temperature requirements, contact information, processing site information, and applicable cautions and warnings. The cell product is sealed in a doubly wrapped sterile bag and placed in a secure transportation box [redacted] to be delivered to the cardiac catheterization facility, [redacted].

[redacted]

11.6 Administration

Upon notification from the cell processing facility that the CLBS16 cell product has been released for infusion (by email), the subject will undergo cardiac catheterization.

[redacted]

The subject will receive standard post cardiac procedure care including repeated examinations of vascular access site for hematomas or local access related complications or retroperitoneal bleed. Subjects will be monitored for 24 hours for

complications, including arrhythmia, ischemia and bleeding from the catheter insertion site.

11.7 [redacted]

[redacted]

11.8 Procedure for unblinding

This is an open label study so a procedure for unblinding is not applicable.

12. STUDY VISIT ASSESSMENTS

[redacted]

12.1 Screening Visits [redacted]

[redacted]

At the first screening visit, perform the following:

- Administer informed consent
- Perform peripheral arterial tonometry
- Review inclusion and exclusion criteria to determine study eligibility
- Collect medical history including demographics (i.e. gender, date of birth, race, and ethnicity)
- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Perform physical examination
- [redacted]
- Collect vital signs
- Collect blood for hematology and clinical chemistry

- Collect blood for lipid panel
- Collect urine and perform urinalysis
- [redacted]
- Collect blood and perform infection tests (including HIV antibody, HBs antigen, HBc antibody, and HCV antibody)
- Perform urine pregnancy test on female subjects of childbearing potential
- Perform 12-lead ECG
- [redacted]

At the second screening visit, perform the following:

- [redacted]
- Perform coronary angiography and coronary microvascular testing if needed (see Supplement 21.7; may be performed on a different day if needed)
- [redacted]
- Assess for adverse events
- Collect information on concomitant medications (including non-drug therapies)
- [redacted]
- Review inclusion and exclusion criteria to confirm study eligibility
- [redacted]

12.2 Pre-treatment Visits [redacted]

The following will be performed or assessed at each of the pre-treatment study days unless noted:

- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Review inclusion and exclusion criteria to confirm study eligibility
- Perform vital signs

- Perform urine pregnancy test on female subjects of childbearing potential (only on pre-treatment Day 1)
- Perform 12-lead ECG (only on pre-treatment Day 1)
- Collect blood for hematology
- [redacted]

12.3 Treatment Visit (Day 0)

12.3.1 Pre-infusion of IP

The following will be performed or assessed approximately 2 hours prior to infusion:

- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Perform targeted physical exam
- Collect blood for hematology and clinical chemistry
- Perform urine pregnancy test on female subjects of childbearing potential
- Perform vital signs
- Perform 12-lead ECG
- Confirm eligibility criteria prior to IP infusion
- If applicable, admit for overnight hospitalization (subjects may be monitored overnight in the hospital at the discretion of the investigator)

12.3.2 IP infusion (*Time 0 hrs*)

- Perform vital signs prior to infusion
- Perform intracoronary infusion of IP [redacted]
- Assess for adverse events

12.3.3 Post-infusion of IP (*Time 2, 4, and 6 hrs*)

The following will be performed or assessed approximately 2, 4, and 6 hours post IP infusion:

- Perform vital signs
- Perform 12-lead ECG (only at the 2 and 6 hour time points)
- Assess for adverse events

12.4 Day 1 visit

- Collect information on concomitant medications (including non-drug therapies)
- Perform vital signs
- Perform 12-lead ECG
- Collect blood for hematology and clinical chemistry
- Assess for adverse events
- Discharge from hospital, if applicable

12.5 Day 8 visit

[redacted] collect information on adverse events and concomitant medications including non-drug therapies.

- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events

12.6 Day 30 visit

[redacted]

- Collect information on concomitant medications (including non-drug therapies)
- Perform vital signs (only if patient makes in person visit)
- Collect blood for hematology and clinical chemistry [redacted]
- Assess for adverse events
- [redacted]

12.7 Day 90 Visit

[redacted] collect information on adverse events and concomitant medications including non-drug therapies. Additionally, the site will have provided [redacted]

[redacted]

- Collect information on concomitant medications (including non-drug therapies)
- Perform vital signs (only if patient makes in person visit)
- Assess for adverse events

12.8 Day 180 visits

[redacted] Also note that these procedures may be performed across more than one visit day, within a span of 7 days.

- [redacted]
- Perform peripheral arterial tonometry
- [redacted]
- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Perform 12-lead ECG
- Perform vital signs
- Collect blood for hematology and clinical chemistry
- Collect blood for lipid panel
- [redacted]
- Perform targeted physical exam
- [redacted]
- Perform coronary angiography and coronary microvascular testing [redacted]
- Perform pregnancy test on females of childbearing potential

12.9 Day 365 visit [redacted]

The subject will receive a phone call from the investigative site to collect information on adverse events and concomitant medications including non-drug therapies.

13. SUBJECT MANAGEMENT

13.1 Informed Consent and Enrollment

Subjects will be enrolled when they have provided informed consent (i.e., signs and dates the informed consent form to participate in the study), met all inclusion and none of the exclusion criteria, and completed the screening phase.

13.2 Subject Identification Code (SIC)

The following series of numbers will comprise the SIC: protocol number (e.g., CLBS16-P01), 3-digit number study site number (e.g., 002) to be provided by the Sponsor, and 3-digit subject number (e.g., 003) reflecting the order of enrollment (i.e., signing the informed consent form). For example, the third subject who signed an informed consent form at study site 002 will be identified as Subject CLBS16-P01-002-003. All study documents [e.g., clinical documentation, sample containers, drug accountability logs, etc.] will be identified with the SIC.

13.3 Screening

Subjects must provide informed consent and meet all inclusion/exclusion criteria and have screening procedures performed within the screening window [redacted]. Subjects who have failed the screening process will be recorded as a screen failure. The study site is responsible for maintaining a screening/enrollment log that includes all subjects evaluated for inclusion in the study. The log also will serve to document the reason for screening failure. All screening data will be collected and reported, regardless of screening outcome.

Re-screening of subjects is allowed, at the discretion of the investigator with prior approval from the study Sponsor, unless there are clinical implications that impact the ability of subject to meet selection criteria change.

13.4 Randomization

This is an open-label study with a single group receiving intracoronary CLBS16 infusion, therefore randomization and blinding do not apply to this clinical study.

13.5 Study Visits

The overall study design is illustrated in Supplement 21.1, Study Flow Diagram. Details on the procedures to be performed at each study visit, including screening, can be found in Section 5. Detail of procedures performed at each study visit can be found in Section 12.

13.6 Recording of Medications and Non-Drug Therapies

Beginning from the time of consent, all medications taken and non-drug therapies received and all concomitant medications taken or administered during the study will be documented in the subject's study records.

13.7 Procedures for Monitoring Subject Compliance

All study procedures are to be performed by the investigator or under his/her designation to a co-investigator or study team member, and thus, no separate procedures will be used to monitor subject compliance.

13.8 Subject Completion/Discontinuation

A subject is considered to have completed the study when he/she ceases active participation in the study because the subject has, or is presumed to have, followed the protocol. Reasons for completion/discontinuation will be reported, including: completed, screen failure, adverse event (e.g., death), discontinuation by subject (e.g., lost to follow-up [defined as 3 documented unsuccessful attempts to contact the subject], dropout), physician decision (e.g., pregnancy, progressive disease, non-compliance with IP/protocol violation(s), recovery), study terminated by Sponsor, or other (reason to be specified by the investigator, e.g., technical problems). As the IP is administered once on the treatment day, subject will be considered as discontinued from the study only if the subject is unable to cooperate with study visits and study measurements. All data available for the subject up to the time of completion/discontinuation should be recorded.

The reason for discontinuation will be recorded, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

Subjects withdrawn or discontinued prior to assessment of efficacy at month 6 may be replaced at the discretion of the Sponsor.

For any subject discontinuation or withdrawal, an attempt will be made to obtain follow-up data, per protocol, through the intended completion of the study, if possible.

14. ASSESSMENTS OF EFFICACY

Note that the efficacy assessments should generally be conducted in the order listed here, [redacted]

[redacted]

14.1 [redacted]

[redacted]

14.2 [redacted]

[redacted]

14.3 [redacted]

[redacted]

14.4 [redacted]

[redacted]

14.5 [redacted]

14.6 Peripheral Arterial Tonometry

Peripheral arterial tonometry (PAT) will be measured according to the method used by Suessenbacher, et al.[44] PAT should be measured in the fasting state (at least 12 hours). Vasoactive drugs should be withheld since bed time on the previous day. Patients are to be asked not to smoke on the day of the examination. Peripheral endothelial function will be assessed using the commercially available EndoPAT device (Itamar Medical Ltd, Caesarea, Israel). With this device, a beat-to-beat plethysmographic record of the finger arterial pulse wave amplitude is captured using pneumatic probes placed on the index finger of each hand. For the assessment of endothelial function, the reactive hyperemia technique is to be used. Measurements are to be obtained for 6 minutes at baseline (at rest) followed by 5 minutes of occlusion of the right upper arm with a sphygmomanometer cuff inflated to a suprasystolic level (50 mm Hg above the initially measured systolic blood pressure). The cuff is then deflated to induce reactive (flow-mediated) hyperemia, which is measured for 5 or more minutes. The left hand remains unoccluded as a reference to correct for systemic changes. The PAT-ratio, which represents endothelial function, is calculated as the ratio between the magnitude of the average postocclusive pulse wave amplitude (1.5 to 2.5 minutes after the release of arterial occlusion) and the average pulse wave amplitude observed over 6 minutes of preocclusion, corrected for systemic changes. A worksheet for PAT measures is provided in Supplement 21.2.

14.7 [redacted]

[redacted]

[redacted]

[redacted]

14.8 Coronary Reactivity Testing

The angiographic method was chosen for coronary reactivity testing and assessment of CFR. The alternative method of measuring CFR by transthoracic echocardiographic Doppler was considered but has several limitations. The increase in velocities in response to adenosine cannot differentiate between the endothelium and non-endothelium increase in coronary blood flow. Thus, the main target of the study may be missed if CLBS16 improves endothelial function or epicardial or microcirculation. The accuracy and the reproducibility of transthoracic echocardiography is a major limitation and highly operator dependent ([redacted]). There are also difficulties in obtaining a good signal in a large number of the patients. The risk of the angiographic procedure is very low.[47]

A detailed description of the coronary reactivity testing is found in Supplement 21.7.

14.9 [redacted]

15. ASSESSMENT OF SAFETY

15.1 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including past surgeries and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

All medications taken and non-drug therapies received from the signing of informed consent until completion/termination will be recorded as concomitant medications and non-drug therapies.

Concomitant medications in general are allowed broadly except in cases where they might represent a hazard for the patient or be indicative of an underlying condition that would put the patient at risk.

[redacted]

15.2 Physical Examinations

At screening and subsequent study visits, a physical examination will be performed. A complete physical exam assessment includes general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. Targeted physical examinations will be symptom-directed. The physical examinations should be performed by the same investigator each time, whenever possible. If an abnormal condition is detected at screening, the condition will be described on the medical history form. At subsequent study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be described on the AE form.

15.3 Clinical Laboratory Parameters

15.3.1 Hematology

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [i.e., red blood cell count], and leukocytes [i.e., white blood cell count]) with differential (i.e., basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelet counts, prothrombin time (PT; sec) or international normalized ratio (INR), and activated partial thromboplastin time (APTT; sec). A limited hematology assessment will be performed on pre-treatment visit days and at the Treatment Visit (Day 0), which will only include the complete blood count (CBC) with differential, and platelet counts. Hematology can be evaluated in either the fed or fasted state.

15.3.2 Clinical Chemistry

The clinical chemistry panel will consist of creatinine, estimated glomerular filtration rate (e-GRF), creatine kinase (CK), electrolytes (sodium, potassium, chloride, calcium, magnesium, and phosphate), bicarbonate, total protein (T-pro), albumin, alanine aminotransferase (ALT), total bilirubin (T-bil), alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), and glucose. If hsCRP is not collected as part of cardiac biomarkers, the C-reactive protein

(CRP) should be collected as part of clinical chemistry. Clinical chemistry will be evaluated in the fasted state.

15.3.3 Lipid Panel

The lipid panel will consist of total cholesterol (T-cho), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG). It will be evaluated in the fasted state.

15.3.4 Urinalysis

The urinalysis panel will consist of protein, occult blood, glucose, urobilinogen, bilirubin, ketones, and sediments.

15.3.5 Pregnancy Testing

Urine pregnancy testing for human chorionic gonadotrophin (hCG) will be performed on females of childbearing potential.

15.3.6 Infection Tests

The following infection tests will be performed: HBs antigen, HBc antibody, HCV antibody, and HIV antibody.

15.4 Vital Signs

Vital signs will include body temperature (°F), respiratory rate (breaths/min), pulse rate (beats/min), systolic and diastolic blood pressure (mm Hg), height (in or cm, only at the screening visit) and weight (lb or kg). Blood pressures should be measured in the sitting position after 5 minutes of rest. Vital signs will be measured at screening, during the Pre-Treatment Period, within 30 minutes before and after administration of IP on Day 0, and at each study visit and at study completion/termination. Vital signs will be collected at Day 90 only if the patient makes an in-person visit. Additionally, blood pressure and pulse rate will be monitored at the following timepoints (these will not be made part of the clinical database):

- Within 30 minutes before apheresis and approximately every 15 minutes during apheresis
- Pulse rate and blood pressure will be monitored approximately every 15 minutes during cardiac catheterization

Vital sign values are to be recorded. For each vital sign value, the investigator will determine whether the value is considered an AE (see definition in Section 15.1). If

assessed as an AE, the medical diagnosis (preferably), symptom, or sign will be recorded on the AE form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

15.5 Adverse Events

All AEs will be recorded from signing the informed consent until study completion or discontinuation. An AE is defined as any untoward medical occurrence in a subject administered IP, regardless of a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP. An AE includes any event, regardless of the presumed causality between the event and the IP.

Any subject experiencing an AE will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically necessary for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated in the opinion of the investigator. Non-serious AEs will be followed until the end of subject participation in the study.

15.5.1 Serious Adverse Event

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

- Outcome is fatal/results in death
- Is life-threatening (at the time of the event)
- Requires hospitalization or results in prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Is a medically important event – that may not be immediately life-threatening or require hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (e.g., infection, allergic reaction, etc.)

Each Serious Adverse Event (SAE) will be followed until resolution, medically stabilized, or 30 days after end of study visit, whichever comes first. All SAEs are to be reported to the Sponsor within 24 hours of becoming aware of the event.

15.5.2 **Non-Serious Adverse Event**

A **non-serious** AE is an AE that does not meet the criteria of a SAE.

15.5.3 **Adverse Events of Special Interest**

The following two adverse events of special interest (AESI) will be collected and tracked in this study:

- Infusions prematurely stopped or paused due to an adverse event
- Infusion-related reactions resulting in discontinuation of infusion or requiring medical treatment

15.5.4 **Severity**

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild
  - The AE is a transient discomfort and does not interfere in a significant manner with the subject's normal functioning level.
  - The AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate
  - The AE produces limited impairment of function and may require therapeutic intervention.
  - The AE produces no sequelae.
- Severe
  - The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern.
  - The AE produces sequelae, which require (prolonged) therapeutic intervention.

15.5.5 **Causality**

Causality is a determination of whether there is a reasonable possibility that the IP is etiologically related to/associated with the AE. Causality to both the IP as well as to the infusion procedure will be assessed. Causality assessment includes, e.g., assessment of temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal

relationship between the IP and the AE using his/her clinical expertise and judgement according to the following most appropriate algorithm for the circumstances of the AE:*

- Not related (both circumstances must be met)
  - Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs
  - Is not related to the IP (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
  - No rational exists for relatedness
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP
  - A more likely alternative etiology exists
  - Some (perhaps weak) rational exits for a relatedness
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP
  - An alternative etiology is equally or less likely compared to the potential relationship to the IP
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP
  - Another etiology is unlikely or significantly less likely
- Definitely related
  - The evidence provides convincing proof of a relationship to the IP

15.5.6 **Reporting for Adverse Events**

All AEs will be recorded from signing the informed consent until study completion or discontinuation. AEs that occur prior to treatment will be considered non-treatment emergent AEs. AEs that occur during or after treatment will be considered treatment emergent AEs. Treatment emergent AEs will be analyzed separately. All AEs will be described using the sign, symptom, or medical diagnosis on the AE form in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions. Each AE will be defined as a SAE or non-serious AE according to the definitions in Section 15.5.1 and Section 15.5.2, respectively. The investigator will evaluate the severity of each AE and the causal relationship of the event to the administration of study product (see Section 15.5.4 and Section 15.5.5, respectively). The outcome and action taken also will be recorded on the AE form. Non-serious AEs

* From CTC-AE version 4.03

will be followed until the end of subject participation in the study. SAEs will be followed until medically stabilized or 30 days after termination visit, whichever occurs first.

ALL SAEs ARE TO BE REPORTED ON THE SERIOUS ADVERSE EVENT REPORT FORM AND FAXED TO THE SPONSOR WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT:
Caladrius Biosciences, Inc.: [redacted]

The investigator shall comply with local Food and Drug Administration (FDA) regulations Code of Federal Regulations Title 21 Section 312 [21CFR 312] and any applicable guidance for reporting any SAEs.

15.5.7 Preexisting Diseases

Preexisting diseases that are present before entry into the study (as described in the medical history) will not be recorded as AEs but will be documented in the subject initial history. Preexisting diseases that manifest with the same severity, frequency, or duration after IP exposure also will not be recorded as AEs but will be documented in the subject initial history. However, when there is an increase in the severity or duration of a preexisting disease, the event must be described as an AE, and recorded on the form.

15.5.8 Assessment of Adverse Events

Each AE will be described on the AE form using the medical diagnosis (preferred), symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions. Each AE will be evaluated by the investigator for:

- Seriousness as defined in Section 15.5.1 and Section 15.5.2
- Severity as defined in Section 15.5.4
- Causal relationship to IP exposure or study-related procedure as defined in Section 15.5.5

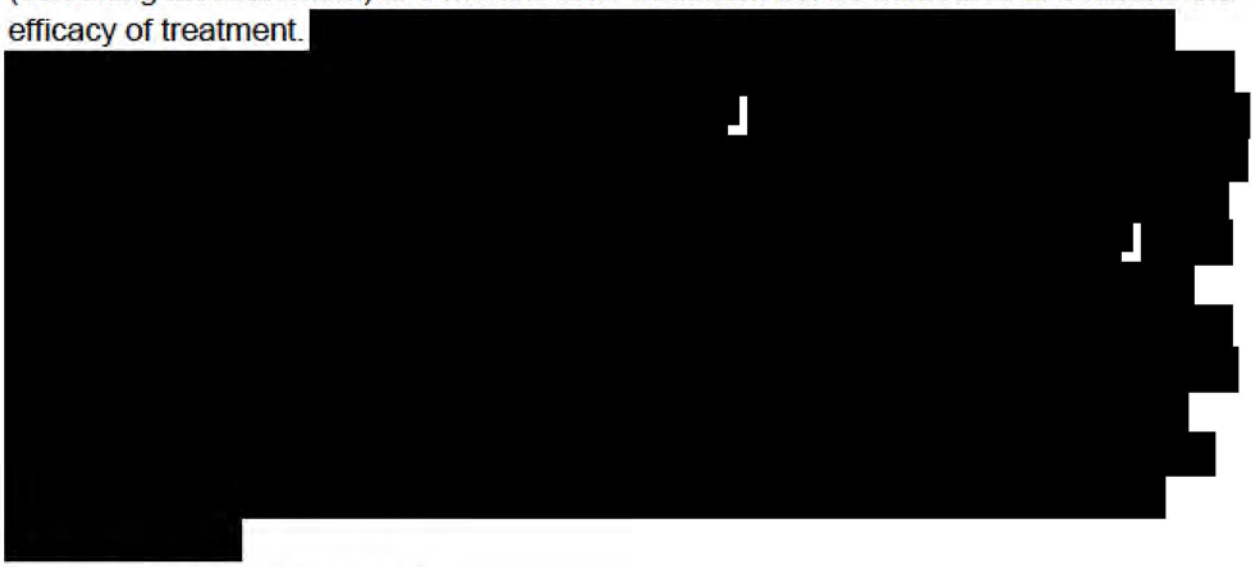
For each AE, the outcome (i.e., recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken

will also be recorded on the AE form. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the patient's termination visit, whichever comes first.

16. STATISTICS

16.1 Sample Size and Power Calculations

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.



16.2 Analysis populations

16.2.1 Safety analysis set

The safety analysis set will consist of all subjects who have been consented in the study

16.2.2 Intent to treat analysis set

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

16.2.3 Per-protocol analysis set

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

16.3 Planned Statistical Analysis

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.

17. DATA HANDLING AND RECORD KEEPING

17.1 Confidentiality Policy

The investigator will comply with the confidentiality policy as described in the Clinical Study Agreement and with national, local, and institution-specific patient privacy regulations.

17.2 Study Documents

The investigator will maintain complete and accurate study documentation in a separate file. Documentation may include medical records, records detailing the progress of the study for each subject, signed informed consent forms, drug disposition records, correspondence with the IRB and the study monitor/Sponsor, enrollment and screening information, data worksheets, SAE laboratory reports (if applicable), data clarifications requested by the Sponsor, etc.

The investigator will comply with the procedures for data recording and reporting. Any corrections to study documentation must be performed as follows: 1) the first entry will be crossed out entirely, remaining legible; and 2) each correction must be dated and initialed by the person correcting the entry and include the reason for change, if not obvious. The use of correction fluid and erasing are prohibited.

Questions or interpretations of the protocol will be referred to the Sponsor. The Sponsor is responsible for providing interpretation of all data questions.

It is recommended that data worksheets be completed within 48 hours of data becoming available.

The investigator is responsible for the procurement of data and for the quality of data. Only designated study site personnel shall record or change data. Each correction will require documentation of the reason for the change.

Any data correction will be noted, including old and new values, initials, and date when authorized study personnel made the change.

17.3 Document and Data Retention

The investigator will retain study documentation and data (paper and electronic) in accordance with 21 CFR §312.57 (for 2 years after a marketing application is approved for the drug or until 2 years after the CLBS16 IND has been deactivated, whichever occurs first) and other applicable national, local, and regional regulatory requirements.

17.4 Direct Access to Source Data/Documents

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the Sponsor or Sponsor's representatives, review by the IRB, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the Sponsor of contact, cooperate with the authority, provide the Sponsor with copies of all documents received from the authority, and allow the Sponsor to comment on any responses, as described in the Clinical Study Agreement.

18. QUALITY CONTROL AND QUALITY ASSURANCE

18.1 Investigator's Responsibility

The investigator will comply with the protocol (which has been approved/given favorable opinion by an Institutional Review Board [IRB]), International Council on Harmonisation (ICH), Good Clinical Practice (GCP), and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term "investigator" as used in this

protocol and in study documents refers to the investigator or authorized study personnel that the investigator has designated to perform certain duties. Sub-investigators or other authorized study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

18.2 Investigator Report and Final Clinical Study Report

The investigator will submit a written report of the study's status to the Sponsor, as described in the Clinical Study Agreement. The investigator will also submit interim progress reports to the Sponsor on a regular basis, as requested.

18.3 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the Sponsor.

18.4 Auditing

The Sponsor and/or Sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, ICH GCP, and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

18.5 Non-Compliance with the Protocol

The investigator may deviate from the protocol to eliminate an apparent immediate hazard to the subject or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of study monitor, change of phone number). In the event(s) of an apparent immediate hazard to the subject, the investigator will notify the Sponsor immediately by phone and confirm notification to the Sponsor in writing as soon as possible, but within 5 working days after the change is implemented. The investigator will also notify the IRB of the emergency change.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the Sponsor may terminate the investigator's participation. The Sponsor will notify the IRB and applicable regulatory authorities of any investigator termination.

19. ETHICS

19.1 Compliance Statement

This study will be conducted in accordance with this protocol, the International Council on Harmonisation Guideline for Good Clinical Practice E6(R2) (09 November 2016), Title 21 of the US Code of Federal Regulations (US CFR), and other applicable national and local regulatory requirements.

19.2 Participating Centers

Participating clinical sites must have an appropriate IRB governance since they are actively engaged in research and provide informed consent. Health Insurance Portability and Accountability Act (HIPAA) and applicable local regulations will be followed by each participating institution in accordance with each institution's requirements. The participating sites will obtain approval from their corresponding review boards in accordance with their local procedures and institutional requirements.

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented.

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants participating in this study. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits.

19.3 Informed Consent

Written informed consent will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. Investigators will enroll patients according to the study eligibility criteria and in compliance with 21 CFR §50 and/or 45 CFR §46. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must sign an informed consent form before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the informed consent form will be reviewed by the Sponsor and approved by an IRB. The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by 21 CFR §50 and/or 45 CFR §46, ICH GCP, and applicable regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the informed consent form, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The Sponsor will provide to the investigator in written form any new information that significantly bears on the subjects' risks associated with IP exposure and study procedures. The informed consent will be updated, if necessary. This new information and/or revised informed consent form, that has been approved by the applicable IRB, will be provided by the investigator to the subjects who consented to participate in the study and are still actively participating.

19.4 Subject Privacy

The investigator will comply with applicable subject privacy regulations/guidance as described in the Clinical Study Agreement.

19.5 Risks and Benefits

The risks of this study are presented in the Investigator's Brochure and the informed consent form. There is no guaranteed benefit to subjects for their participation in the study.

19.6 Ethics Committee and Regulatory Authorities

Before enrollment of patients into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided to the patients will be reviewed and approved/given favorable opinion by an IRB. The Investigator's Brochure will be provided for review. The IRB's composition or a statement that the IRB's composition meets applicable regulatory criteria will be documented. The study will commence only upon the Sponsor's receipt of approval/favorable opinion from the IRB, as described in the Clinical Study Agreement.

If the protocol or any other information given to the subject is amended, the revised documents will be reviewed and approved/given favorable opinion by the IRB. The protocol amendment will only be implemented upon the Sponsor's receipt of approval

and, if required, upon the Sponsor's notification of applicable regulatory authority(ies) approval.

20. STUDY ADMINISTRATION

20.1 Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include telephone calls and on-site visits. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site visits, the collected data will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor may periodically request review of the investigator study file to assure the completeness of documentation in all respects of clinical study conduct.

The study monitor will verify that each patient has proper consent documentation from the patient and/or patient's authorized representative for study procedures and for the release of medical records. The investigator or appointed delegate will receive the study monitor during these on-site visits and will cooperate in providing the documents for inspection and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of regulatory agencies.

On completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period.

20.2 Medical Monitor

All adverse events will be recorded on the adverse event forms, and the treatment related SAEs will be sent to the IRB, per their reporting requirements, and to the Sponsor. The study medical monitor or designee will review all adverse event reports. Further details are captured in the study medical monitoring plan.

20.3 Financing and Insurance

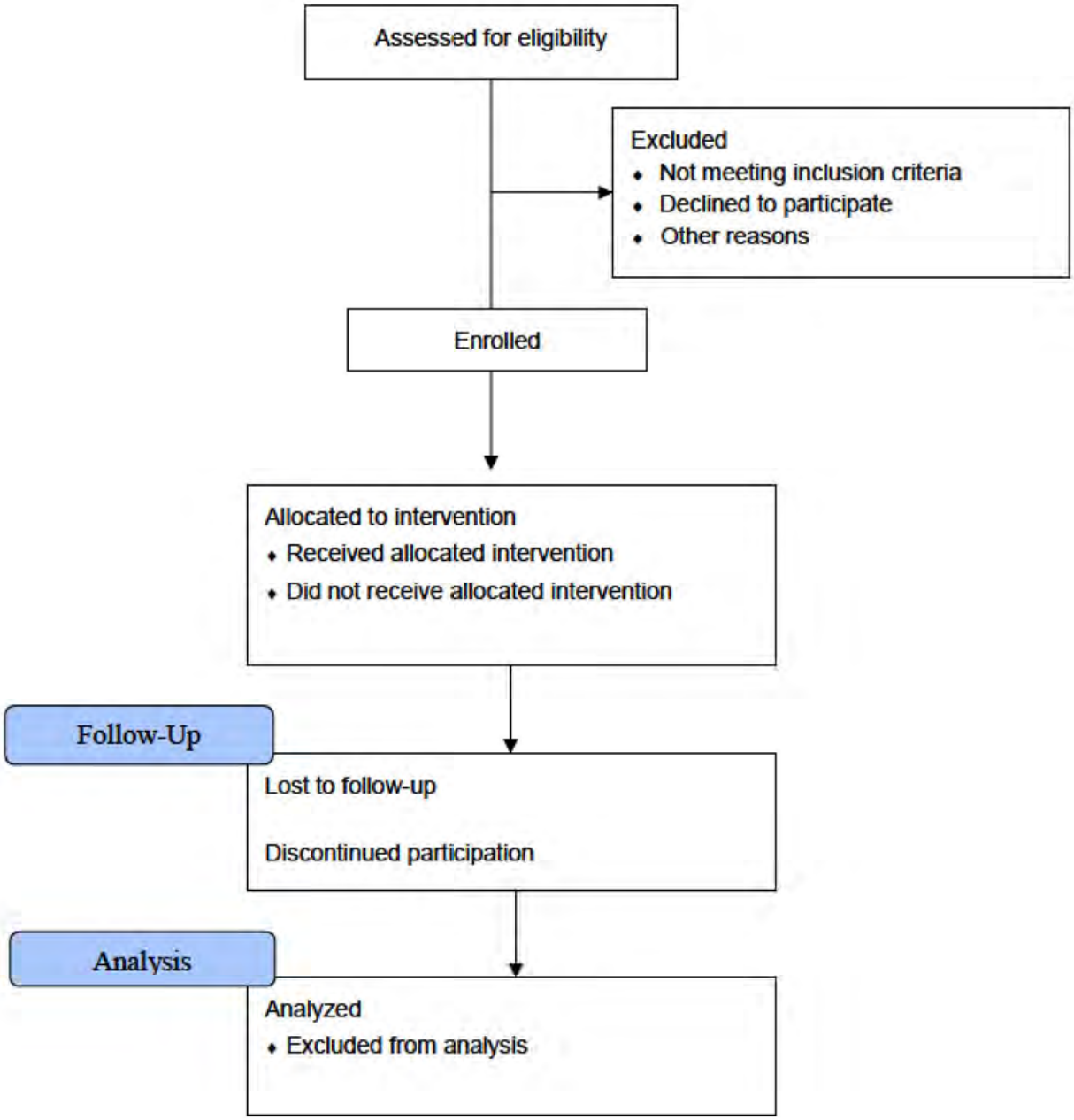
The investigator will comply with investigator financing, investigator/Sponsor insurance, and subject compensation policies, if applicable, as described in the Clinical Study Agreement.

20.4 Publication Policy

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

21. SUPPLEMENTS

21.1 Study Flow Diagram



21.2 Peripheral Arterial Tonometry Worksheet

Patient ID: _____ Patient Initials ___ ___ ___

Date: ___/___/_____ Time: ____:____ Dominant Arm: Right ☐ Left ☐

Sex: Male ☐ Female ☐ Age: _____ Arm Occluded (non-dominant): Right ☐ Left ☐

Room Temp: _____°F @ beginning of test

Blood pressure #1 _____ /_____ (mm Hg) HR _____ (beats/min)

Blood pressure #2 (if necessary) _____ / _____ (mm Hg) HR _____ (beats/min)

CHECKLIST FOR TEST PREPARATION

Room:

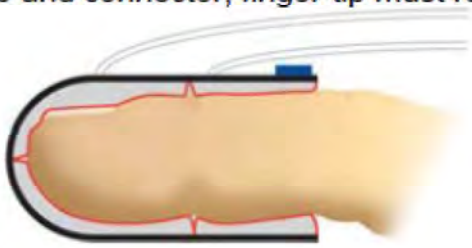
- ☐ Device setup: turn on 20 minutes prior, close to bed, avoid biofeedback, PC screen turned away from patient
- ☐ Accessories: micropore tape, thermometer, armrest, blood pressure cuff
- ☐ Environment check:
  - Temperature 70-75°F, pt 20 minute acclimatization, no breeze
  - Noise: quiet room, mobile phones off, patient should avoid talking during test
  - Light: avoid harsh light, room should be dim

Patient:

- ☐ Patient check: encourage patient to go to the restroom (avoid washing hands in cold/warm water), remove jewelry, watches and rings; avoid heavy/tight-fitting clothing, finger nails trimmed, cover patients who are cold
- ☐ Explain test to patient: 20 minutes, 3 phases, harmless but may be uncomfortable, after occlusion test is not over
- ☐ Place subject in supine position
- ☐ Measure patient blood pressure from dominant arm (non-tested arm) – snug but not too tight
- ☐ Ask subject to refrain from moving fingers; keep fingers relaxed not touching anything
- ☐ Insert patient details: ID, age, sex, diastolic pressure (up to 80 mm Hg), remark 1 = room temperature setting remark 2 =fingernail condition Long => 0.5cm, OK = Trimmed, PATographer

Assemble:

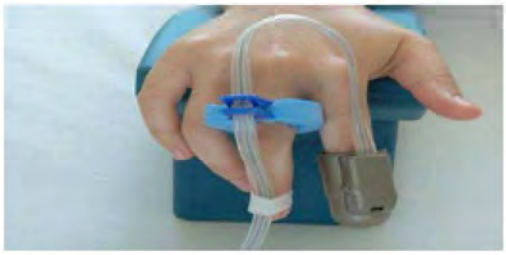
- ☐ Probes assembly: (connect a new set of probes to the tubes)
    1. Click "Deflate"
    2. Insert probe into groove in the arm-support
    3. Select finger (preferably the index finger. Very large fingers – use little finger; use same finger on both hands)
    4. Apply probes: insert test finger into DEFLATED probe (make sure to align the top of the finger with the probe and connector; finger-tip must reach all the way to the end of the probe).



    5. Click "Inflate"
    6. After inflation is completes the finger with the probe attached can be removed from the groove.
    7. Apply blue foam anchors on the adjacent finger (tubes should not cross) and push to the root of the finger.
    8. Secure tube by taping the free end in an "S" shape to maintain anchor perpendicular to finger axis.

- ☐ Reposition patient:
    1. The forearm should be placed on the Arm-support palm-side down
    2. The hand should be placed over the edge of the support so the fingers dangle freely.

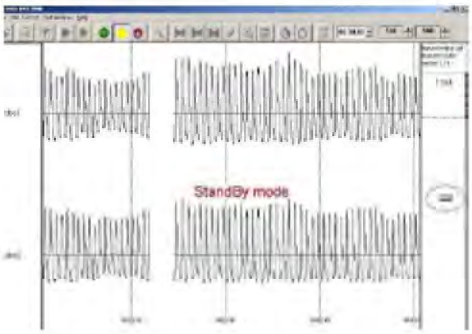
  The probe should not touch:
    - Adjacent finger
    - Foam anchor
    - Thumb
    - Arm support
    - Anything



Testing:

- ☐ Pre-recording/Signal Quality

1. Click "Standby"
2. Adjust gain for optimal signal view
3. Inspect signal quality for 1-2 minutes
4. Tap on designated occluded (arm with BP cuff) to determine Probe 1 and Probe 2
5. Make sure there are no leaks for at least 1 minute, refrain from talking to patient and other staff



Please take note of:

- ☐ **Screen:** After good signal strength for at least 1 minute
- ☐ Patient: should be relaxed, fingers free and still
- ☐ Nothing should touch the probe during the test
- ☐ A recording signal icon should appear pointing at the hard drive

Phase 1—Baseline

- ☐ Click "Go"
  - Baseline start time: ____:____:____
- ☐ Record for 6 minutes before occlusion
- ☐ If leaks or problems occur during the baseline; it is still OK to stop the study, replace probes and start over.

- ☐ **Just before occlusion**
  Adjust gain of designated occluded arm to 20,000
  Inform patient that you are about to occlude for 5 minutes.

Phase 2 - Occlusion

- ☐ Occlusion Recording 5 minutes
  RAPIDLY inflate the BP cuff – 60 mm Hg above systolic BL not less than 200 mm Hg and not above 300.
  Start countdown clock icon in the menu bar
  Check the signal of the test arm for incomplete occlusion
  If occlusion is incomplete, increase pressure by 50 mm Hg, up to 300 mm Hg

- ☐ Mark start time:
  - Occlusion start time:____:____:____
  - Occlusion end time:____:____:____
- ☐ Occlusion Release
  After exactly 5 minutes
  Rapidly release
  Lower gain of occluded arm to fit screen

Phase 3—Test End

- ☐ Post Occlusion: change gain back
  Record 5 minutes post occlusion (no less than 5 minutes)
  Inform patient that you are about to end the study
  Click "Stop"
  Probes will deflate automatically, remove used probes, tape and discard
  Remove cuff

Blood pressure #3: ____ / _____ (mm Hg) HR _____ (beats/min) Room Temp @ end of test: _____ °F

Result (RHI): _____ Number of Leaks: _____

Comments:

PAT performed by: (please print)

_____

Signature: _____ **Date:** ___/___/_____

21.3 [redacted]

[redacted]

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21.4 [redacted]

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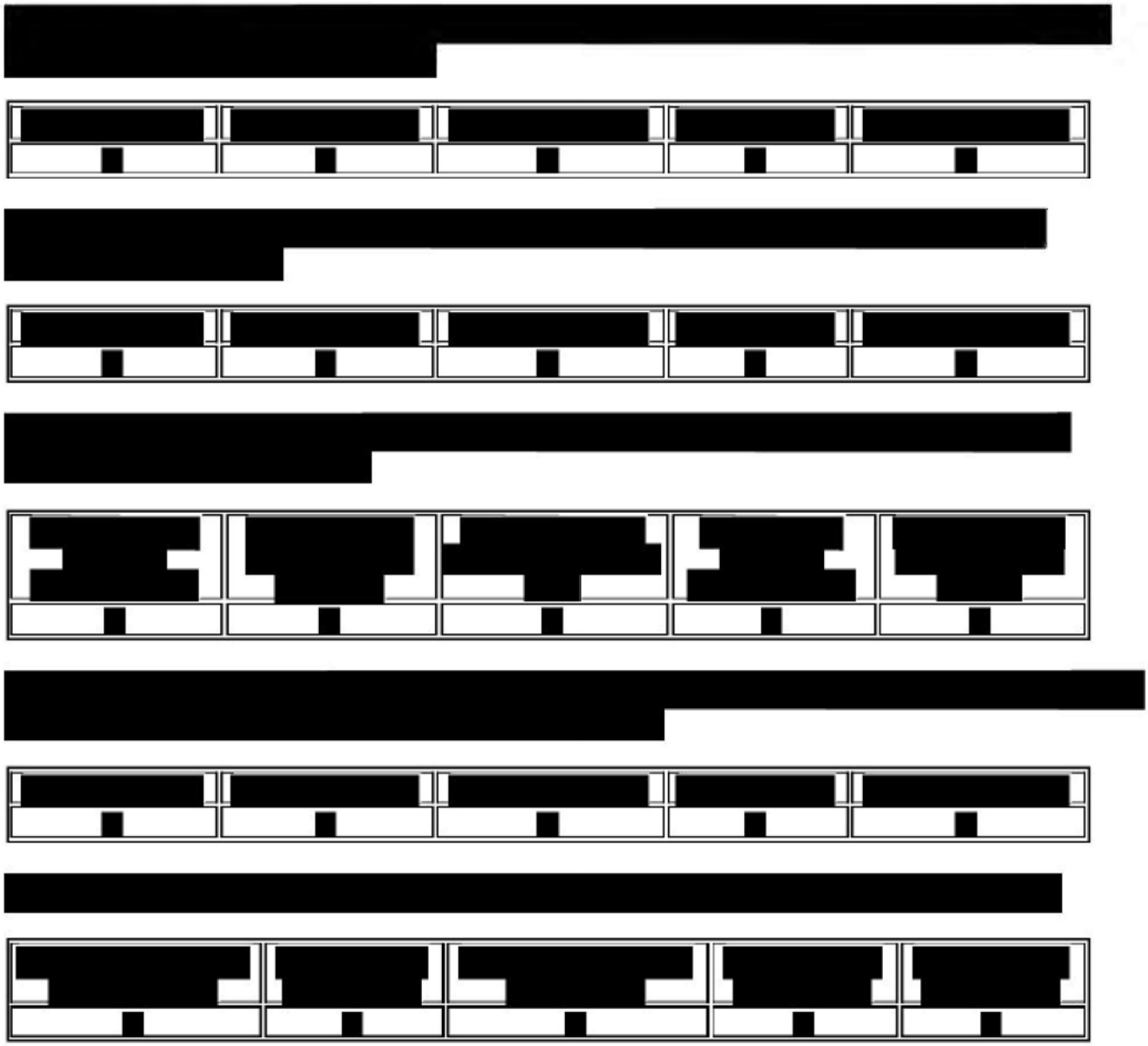

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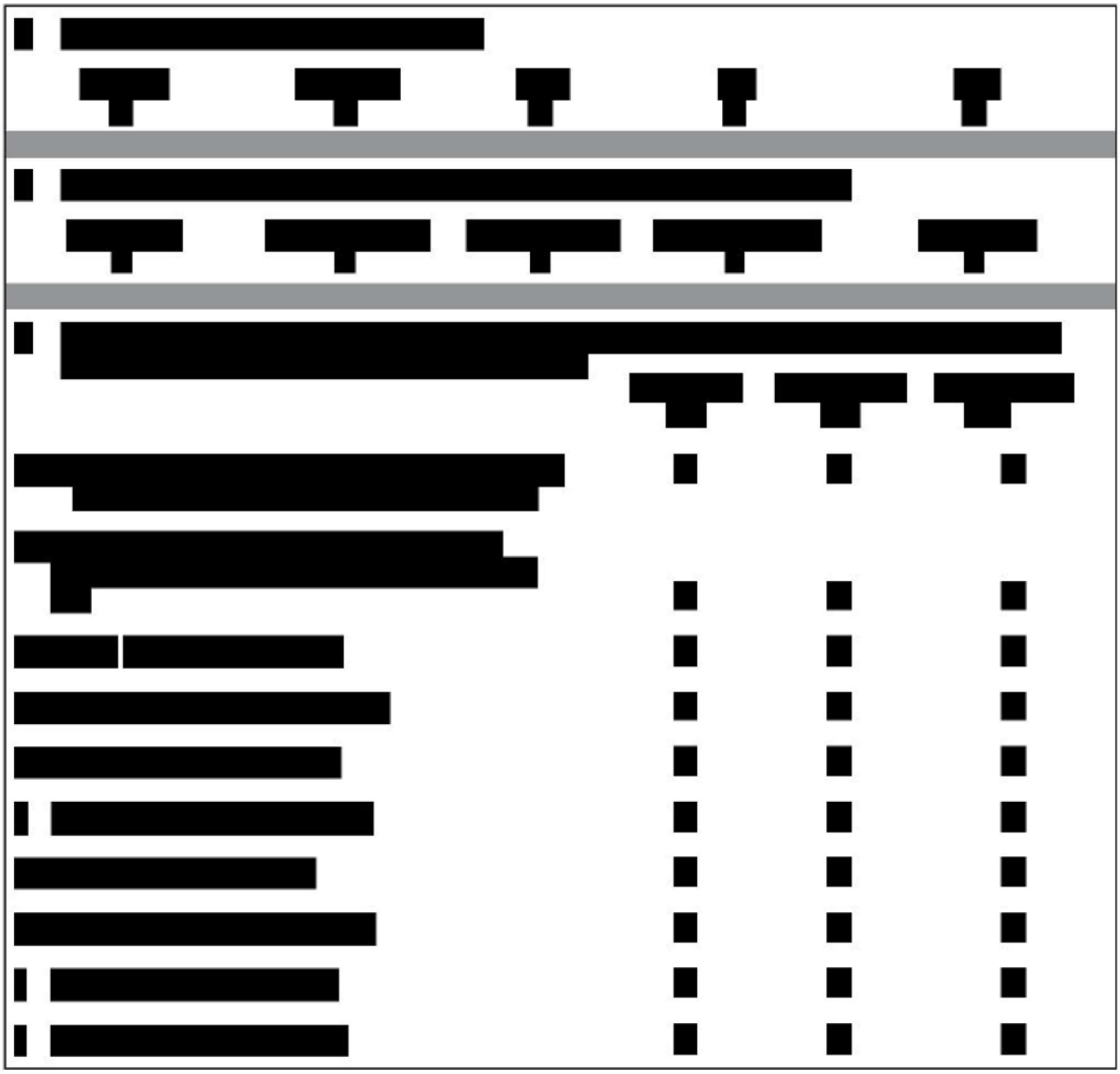

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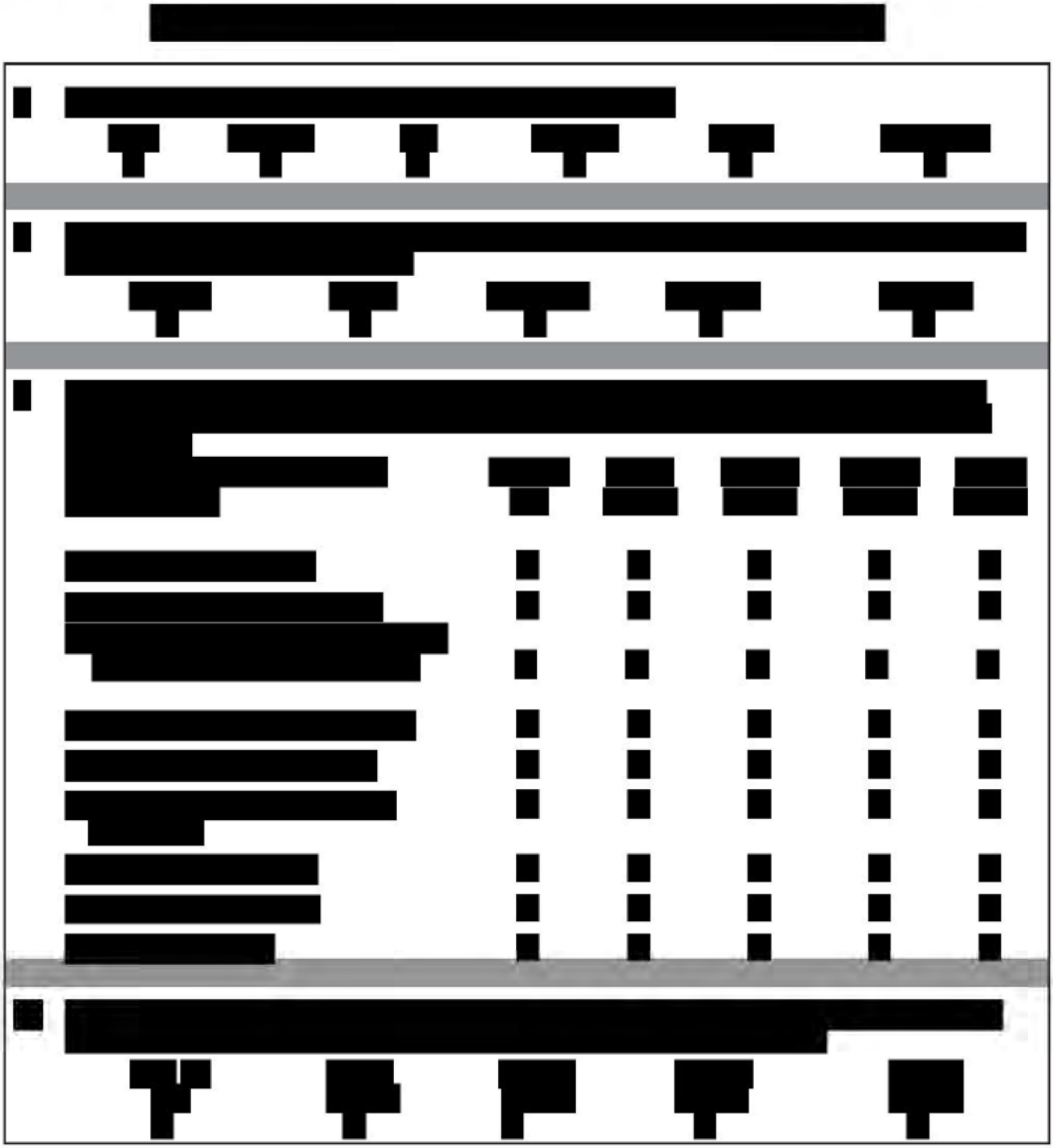

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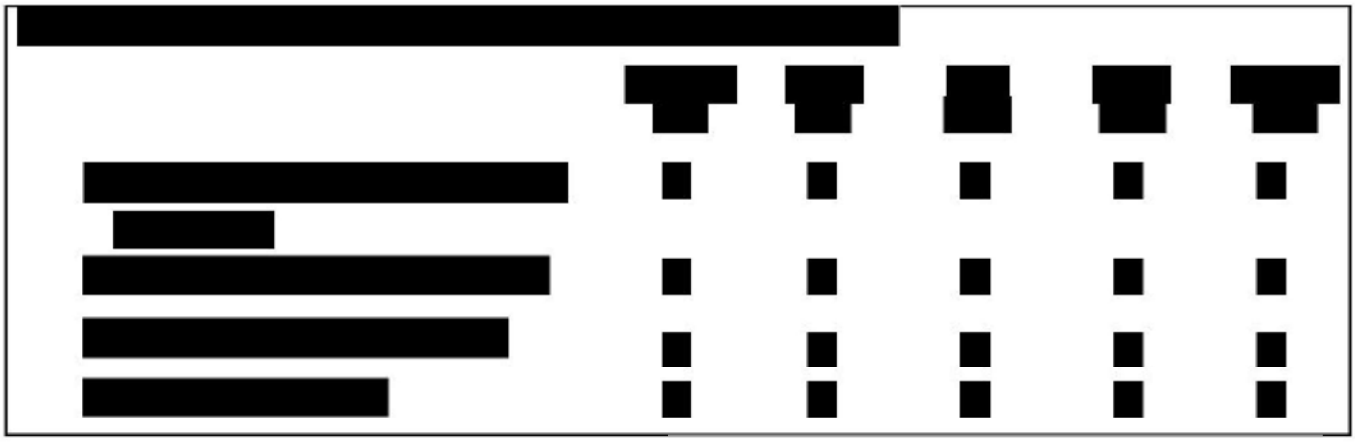

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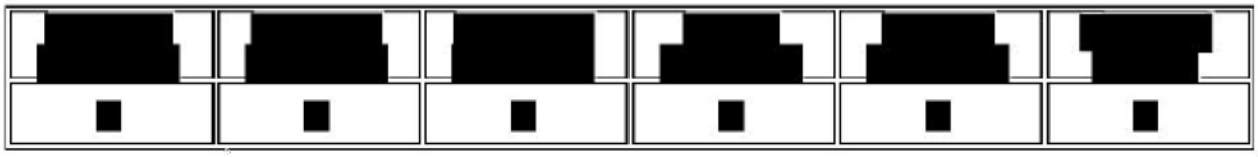

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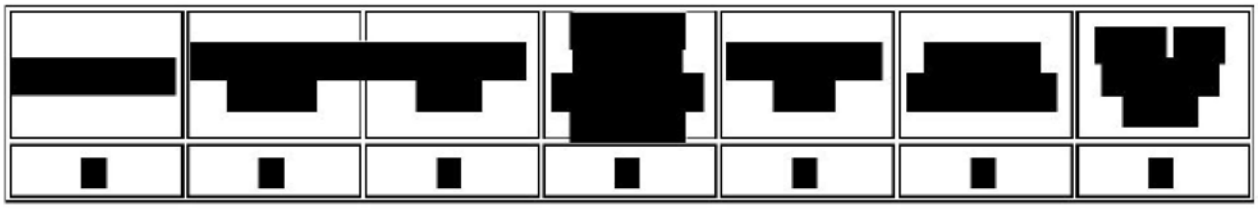

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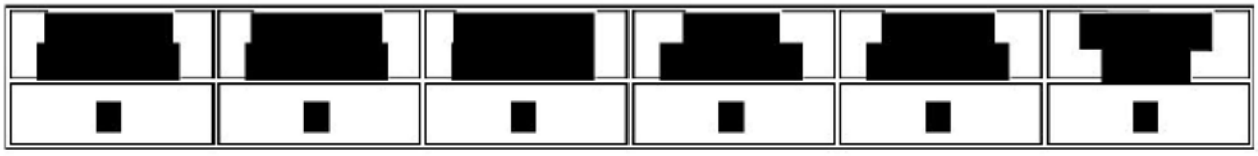

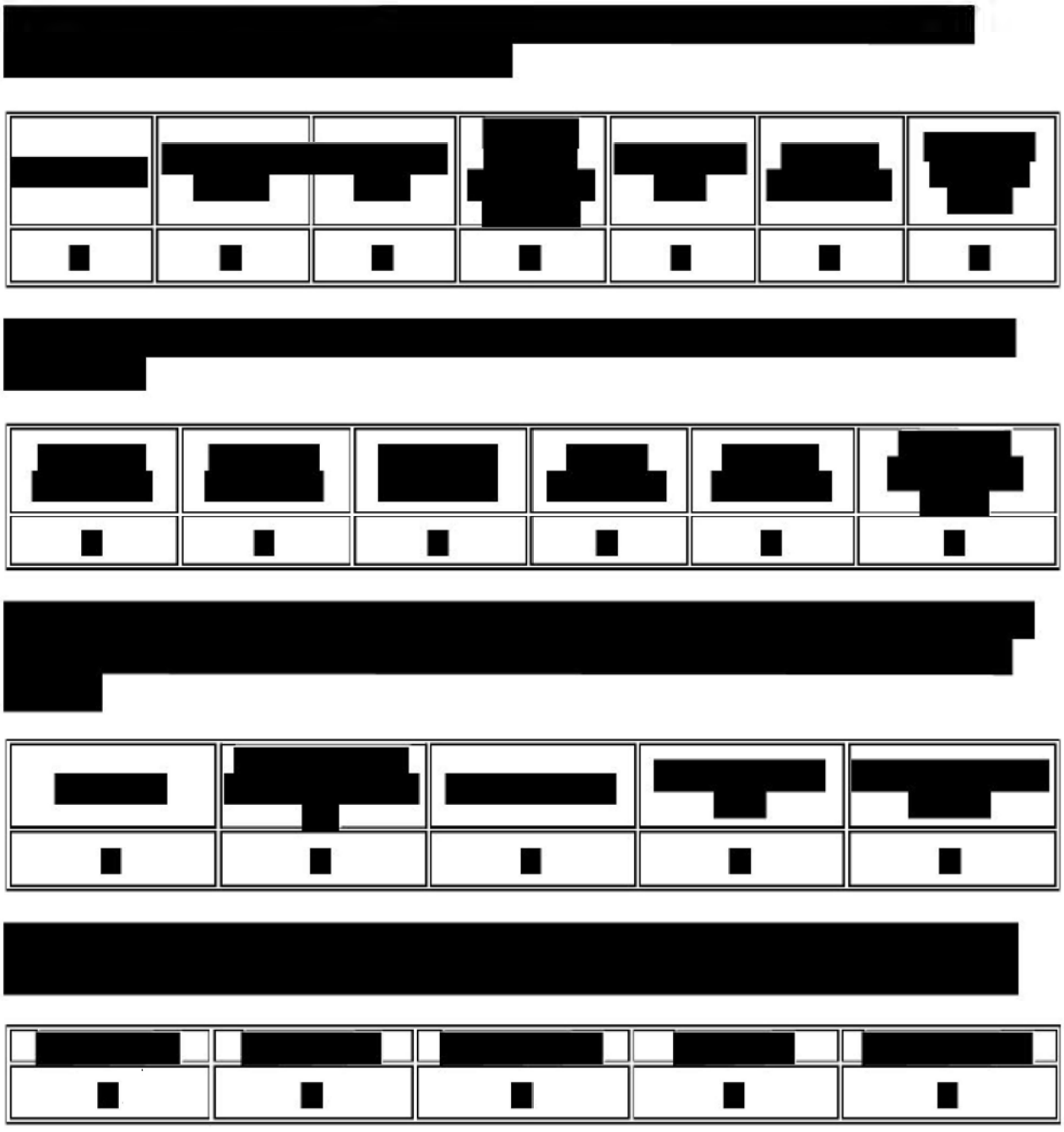

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21.7 Invasive Coronary Reactivity Testing – Screening and Month 6

Screening (if needed) and Month 6 CRT will be performed [redacted]

Pre-Angiogram CRT Instructions

1. Please fast before your appointment.
   - Nothing to eat or drink for 12 hours prior to your appointment (except you may drink water.
   - No caffeine 24 hours prior to your appointment whenever possible (i.e. tea, coffee, chocolate, soda, Anacin/Excedrin).
2. Please discontinue your use of:
   - Nicotine 4 hrs prior to your appointment
   - Long-acting nitrates, short-acting calcium channel blockers, alpha blockers and beta blockers, ACE/ARB inhibitors, Renin and Aldosterone Inhibitors for 24 hours prior to your testing whenever possible
   - Long-acting calcium channel blockers for 48 hours prior to your testing.
   - Sublingual nitroglycerin for 4 hours prior to your testing.
   - Bring your medications with you so that you can take them after the procedure.

Cath Lab requirements

1. Catheter size (e.g. 6 Fr) must be indicated
2. Flags on all cine runs
3. Obtain baseline angio (contrast injection) with the flow-wire in place
4. [redacted]
7. 12-lead EKG recording during infusions to evaluate for ST/T changes and documentation of chest pain

Diagnostic Coronary Angiography

1. Insert 7F sheath in the femoral artery.
2. Diagnostic left and right coronary angiography
3. Measure LVEDP using pigtail catheter

Coronary Reactivity Testing

1. Once equipment is set up and flow wire is in position start the Volcano Machine timer (Press Baseline 2 times to start timer).
2. Set Volcano Machine to either "Split screen" or "full screen" view according to local preference.

[redacted]

2. Investigator to choose vessel for testing. Make sure the vessels are not overlapping, ECG leads are not obstructing view and vessel is adequately filled when obtaining cine images.
3. Take baseline Angiogram marked as "Baseline"
4. Record baseline Cine View this includes documentation of angles and cath size being used
5. Set Doppler in CFR mode

[redacted]

   a. Record baseline blood pressure/heart rate
   b. Press "Baseline" on Volcano Machine/Record baseline APV

[redacted]

   d. Record infusion time
   e. Flush
   f. wait 5 seconds
   g. Press "PEAK" on Volcano Machine
   h. Wait for peak CFR to appear.
   i. Record peak blood pressure/heart rate/ Peak APV/CFR
   j. Press print.

[redacted]

   a. Record baseline blood pressure/heart rate
   b. Press "Baseline" on Volcano Machine/Record baseline APV

[redacted]

   d. Record infusion time
   e. Flush
   f. wait 5 seconds
   g. Press "PEAK" on Volcano Machine
   h. Wait for peak CFR to appear.
   i. Record peak blood pressure/heart rate/ Peak APV/CFR
   j. Press print.

[redacted]

a. Record baseline blood pressure/heart rate
b. Press "Baseline" on Volcano Machine/Record baseline APV
[redacted]
d. Record infusion time
e. Flush
f. wait 5 seconds
g. Press "PEAK" on Volcano Machine
h. Wait for peak CFR to appear
i. Record Peak blood pressure/heart rate/ Peak APV/CFR
j. Press print.

[redacted]

NOTE 1: May repeat any of the doses at the investigator's discretion
NOTE 2: The highest CFR value from all the measurements will be used to qualify the subject for eligibility

[redacted]

2. To program machine, press "System On"
3. "New Patient" – press Yes
4. "Telemetry" or "Adult ICU" – press Yes
5. Machine will auto-detect syringe. Select syringe and press "Confirm"
6. Select "Rate" and enter 60 (mL/hr)
7. Select "VTBI" and enter 2.4 (mL)
8. Press "Options" – select "Anesthesia Mode" – select "Enable"
9. Press "Start" to start infusion
10. When infusion is complete, pump will beep. Press "Silence"

[redacted]

reconnect tubing
12. Press "Channel select" on pump
13. IV machine will prompt again for syringe, select and "Confirm"
14. Press "Restore"
15. Press "Start" to begin second infusion

[redacted]

NOTE: Infuse into the catheter dead space 3.5 cc (infusion catheter space: 3 cc; infusion stopcock: 0.5 cc)

1. Set Volcano on "Trend Mode"
2. Make sure pump is attached to the IV pole and hand sterile tubing to angiographer

[redacted]

5. Select the syringe size (usually only choice of BD 10 cc syringe) and press "Confirm"
6. Enter infusion rate "60" cc/hr (this will distribute the dose over 3 minutes) and VTBI "2.4" cc (this will deliver 2 cc intracoronary)

[redacted]

[redacted]

   a. Record baseline blood pressure/heart rate
   b. Press Baseline on Volcano Machine/Record baseline APV
   c. Start timer for 3 min/record time on Volcano Machine

[redacted]

   e. Image Cine Marker during infusion- "ACH low" or "10-6"
   f. At 2:50 minutes press PEAK on Volcano Machine
   g. Wait for peak CFR to appear
   h. Record Peak blood pressure/heart rate/ Peak APV/CFR
   i. Press print

[redacted]

   in the infusion catheter prior to cine
   k. Take cine image

[redacted]

10. Press "Channel Select" again once loaded, and "Confirm" syringe (20 cc syringe)
11. Press "Restore" for prior settings and "Start" when ready to infuse

[redacted]

[redacted]

   a. Record baseline blood pressure/heart rate
   b. Press Baseline on Volcano Machine/Record baseline APV
   c. Start timer for 3 min/record time on Volcano Machine

[redacted]

f. At 2:50 minutes press PEAK on Volcano Machine
g. Wait for peak CFR to appear
h. Record Peak blood pressure/heart rate/ Peak APV/CFR
i. Press print
j. Angiographer will clear 3 cc of high-dose acetylcholine prior to cine
k. Take cine image

[redacted]

1. Set Volcano to "Split screen"
2. Place Cine Marker- "NTG"
3. Record baseline blood pressure/heart rate
4. Press Baseline on Volcano Machine/Record baseline APV

[redacted]

6. Flush
7. At 30 seconds press "PEAK" on Volcano Machine
8. Wait for peak CFR to appear.
9. Record peak blood pressure/heart rate/Peak APV/CFR
10. Press print
11. Take Cine Image immediately after Peak APV/CFR is recorded

21.8 Cell Delivery Protocol

Pre-Angiogram Cell Delivery Subject Instructions

1. Please fast before your appointment.
    - Nothing to eat or drink for 12 hours prior to your appointment (except you may drink water).
2. Please discontinue your use of:
    - Nicotine 4 hrs prior to your appointment
    - Bring your medications with you so that you can take them after the procedure.

Cath Lab requirements

1. Catheter size (e.g. 6 Fr) must be indicated
2. Obtain LAD baseline angio (contrast injection)
3. Infusion catheter will be the LAD seating catheter

Cell Delivery

The general procedure for administration of CLBS16 is provided below. Please refer to the investigational product manual for this protocol for specific details.

[redacted]

22. SIGNIFICANT CHANGES FROM PROTOCOL VERSION 6

[redacted]

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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

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By signing below, the investigator acknowledges that he/she has read and understands this protocol and provides assurance that this study will be conducted according to all requirements as defined in this protocol, clinical study agreement, ICH GCP guidelines, and all applicable regulatory requirements.

Investigator Signature Date

Print Name and Title of Investigator