CLINICAL STUDY PROTOCOL

CLBS16

PHASE 2

A Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of CLBS16 in Subjects with Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease

PROTOCOL NUMBER: CLBS16-P02

ClinicalTrials.gov Identifier: NCT04614467

Version Number: 9

Version Date: 3 December 2021

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

PROTOCOL APPROVAL FORM

CLINICAL STUDY PROTOCOL

CLBS16-P02

A Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of CLBS16 in Subjects with Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease

ClinicalTrials.gov Identifier: NCT04614467

Version Number: 9

Version Date: 3 December 2021

APPROVAL SIGNATURES:

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]	**Alternate Study Contact** [redacted]

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

PROTOCOL VERSION 9 SUMMARY OF KEY CHANGES

The following sections have been amended:

Description of Change	Applicable Section Numbers
A 12-month assessment time point was added to collect information on angina frequency, nitroglycerin use, CCS angina class, quality-of-life, and adverse events	Synopsis, Sections 4.3, 4.4, 5.1, 8.9, and 8.10

In addition to the changes above, the CLBS16-P02 protocol may have been edited for style, formatting, clarity, and consistency.

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-P02
PROTOCOL TITLE	A Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of CLBS16 in Subjects with Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease
Short Title	CLBS16 for Coronary Microvascular Dysfunction
STUDY PHASE	2
STUDY OBJECTIVES AND PURPOSE	
Study Purpose	
To evaluate the efficacy and safety of autologous CD34+ cells (CLBS16) in subjects with coronary microvascular dysfunction (CMD) and without obstructive coronary artery disease	
Efficacy Objectives	
To evaluate the effect size and variability of CLBS16 in subjects with CMD and without obstructive coronary artery disease on angina frequency, exercise tolerance test (ETT), Canadian Cardiovascular Society (CCS) angina classification, and quality of life.	
Safety Objectives	
To evaluate the safety of CLBS16 in subjects with CMD and without obstructive coronary artery disease.	
STUDY DESIGN	
Study Type	Interventional
Control Type	Placebo
Study Classification	Efficacy/Safety
Blinding Schema	The comparison of active CLBS16 treatment versus placebo treatment will be double-blind – subjects, investigators, and Sponsor personnel will remain blinded to treatment assignments.

Study Design	This is a phase 2 randomized, double-blind, and placebo-controlled clinical study to evaluate the efficacy and safety of CLBS16 in subjects with CMD and without obstructive coronary artery disease. **Screening Phase** Subjects who provide informed consent will be screened for eligibility within 60 days before beginning the study treatment phase. All subjects must have a diagnosis of CMD based on a coronary microvascular assessment as outlined in Section 6. Briefly, a diagnosis of CMD can be based on any of the following thresholds: coronary flow reserve (CFR) ≤2.5, coronary blood flow (CBF) response to acetylcholine ≤50%, myocardial perfusion reserve (MPR) or myocardial flow reserve (MFR) <2.0, or index of microvascular resistance (IMR) > 25. A coronary microvascular assessment prior to the study is allowed if it occurred within 180 days prior to the first screening visit. Any cardiovascular medical therapy must be at a stable dose for at least 30 days prior to the first screening visit and must be maintained at that dose throughout the duration of the study; cardiovascular therapy would generally include statins (unless not tolerated), angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB)s, beta blockers, calcium channel blockers, and/or ranolazine (unless ineffective or not tolerated). Baseline angina and nitroglycerin diary, Health Related Quality of Life (HRQoL), and ETT will also be assessed. Approximately 105 eligible subjects will be randomized to receive CLBS16 or placebo in a 4:3 ratio (60 CLBS16 vs 45 Placebo) **G-CSF and Treatment Phase** All research subjects will receive subcutaneous injections of G-CSF at a dose of 5 µg/kg/day for 5 days to mobilize CD34+ cells into the peripheral blood. White blood cell counts in peripheral blood will be assessed on the last day of G-CSF administration. If the white cell count exceeds 75,000 cells/µL on G-CSF Day 5, the final dose of G-CSF will not be given. On G-CSF Day 5, just prior to apheresis, peripheral blood will be collected, which will be used for processing autologous serum, to be used in formulating the investigational product (IP). Subjects will then undergo apheresis to collect CD34+ cells. CD34+ cells will be isolated using the CliniMACS System (Miltenyi Biotec). CD34+ cells (CLBS16) or placebo will be delivered via IC administration (Section 18.4). Non-heparin anticoagulant (e.g., bivalirudin) will be administered to achieve an active clotting time (ACT) of >200 seconds during the procedure. **Observation Phase** All efficacy assessments will be performed through 6 months after treatment to evaluate the potential bioactivity of CLBS16 or placebo in

	subjects with coronary microvascular dysfunction. Select efficacy assessments, which may not require an in-person visit (angina frequency, nitroglycerin use, CCS angina class, SAQ, and SF-36) will also be collected at 12 months. At the discretion of the investigator, assessment of coronary microvascular function may be performed at 6 months after administration of CLBS16 or placebo. If this assessment is performed, it should be with the same methodology used for this assessment at baseline. The occurrence of adverse events (AE)s, SAEs and MACE will be collected for all subjects during the treatment and 6-month follow-up periods to evaluate the safety and tolerability of CLBS16 or placebo. Cardiac-related AEs, SAEs and MACE will also be collected for subjects who undergo an assessment at 12 months.
Planned Duration of Subject Participation	Up to approximately 14 months

Endpoints

Efficacy Endpoints

- Change from baseline in angina frequency at 3, 6, and 12 months captured by angina diary
- Change from baseline in Canadian Cardiovascular Society (CCS) angina class at 3, 6, and 12 months
- Change from baseline in total exercise time and peak metabolic equivalent of task (MET) as measured by ETT using the modified Bruce protocol at 6-months
- Change from baseline in HRQoL as measured by the Seattle Angina Questionnaire (SAQ) and Short Form-36 (SF-36) at 3, 6, and 12 months
- Proportion of subjects with ETT-induced angina at 6 months
- Proportion of subjects with ETT-induced ST-segment changes at 6 months
- Change from baseline in nitroglycerin use at 3, 6, and 12 months

Safety Endpoints

- AEs, including SAEs
- Laboratory investigations
- Physical examinations
- Vital signs
- MACE
- Death

Exploratory Endpoints

- Change from baseline in time to onset of angina and time to ST segment changes during ETT

• Change from baseline in CFR at 6 months in a subset of subjects • Change from baseline in MPR or MFR at 6 months in a subset of subjects • Change from baseline in IMR at 6 months in a subset of subjects • Change from baseline in CBF at 6 months in a subset of subjects	
INVESTIGATIONAL PRODUCT(S), DOSE AND MODE OF ADMINISTRATION	
Investigational Product(s)	**Dosage form**: Solution/Suspension **Dosage frequency**: Once **Dosage**: 1 x 10^6 to 300 x 10^6 CD34+ cells or placebo in a volume of 10 mL Autologous CD34+ cells will be suspended in an isotonic solution with autologous serum and human serum albumin. Placebo will consist of an isotonic solution with autologous serum and human serum albumin.
Mode of Administration	Infusion of CLBS16 or placebo into a coronary artery will be performed in the cardiac catheterization laboratory.
SUBJECT SELECTION	
Planned # Subjects	Approximately 105
Population to be Studied	Men and women 18 years of age and older with CCS class II, III, or IV and without obstructive disease on coronary angiogram within 6 months prior to screening or during screening will be studied. All subjects must have a diagnosis of CMD based on a coronary microvascular assessment as outlined in Section 6. Briefly, a diagnosis of CMD can be based on any of the following thresholds: coronary flow reserve (CFR) ≤2.5, coronary blood flow (CBF) response to acetylcholine ≤50%, myocardial perfusion reserve (MPR) or myocardial flow reserve (MFR) <2.0, or index of microvascular resistance (IMR) > 25. A coronary microvascular assessment prior to the study is allowed if it occurred within 180 days prior to the first screening visit. Subjects who have a history of effort-induced anginal symptoms and currently experience angina will be eligible for the study. Subjects with any prior history of coronary artery bypass graft (CABG), evidence of obstructive heart disease, percutaneous intervention (PCI) (within 6 months prior to consent) or diagnosis of specific cardiac disease such as severe valvular heart disease will be excluded from the study. Subjects experiencing a myocardial infarction within 90 days prior to consent or between consent and treatment with CLBS16 or with a left ventricular ejection fraction (LVEF) < 30% will be excluded.

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, despite maximally tolerated doses of antianginal medications, statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and other medications thought to positively impact subjects with CMD.
3. Diagnosis of CMD based on the following physiological assessments: coronary flow reserve (CFR) ≤2.5, coronary blood flow (CBF) response to acetylcholine ≤50%, myocardial perfusion reserve (MPR) or myocardial flow reserve (MFR) <2.0, or index of microvascular resistance > 25. Physiologic assessments within 180 days prior to or during the screening period are accepted.
4. *
5. CCS class II, III, or IV chronic refractory angina as evaluated by the site
6. No obstructive disease on coronary angiogram within 6 months prior to or during screening. The following is allowed: a coronary artery stenosis less than 40% in the left main coronary artery, or a stenosis less than 50% in any other epicardial coronary artery.
7. If subject is of childbearing potential, the subject must have a negative pregnancy test at screening and prior to mobilization and G-CSF treatment, and prior to receiving treatment. The subject agrees to employ adequate birth control measures for the duration of the study. Acceptable methods of birth control are: oral contraceptive tablets, hormonal implant device, hormonal patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, partner vasectomy, or abstinence.
8. Subject is willing and able to comply with the requirements of the protocol
9. Any cardiovascular medical therapy must be at a stable dose for at least 30 days prior to the first screening visit and must be maintained at that dose throughout the duration of the study; cardiovascular therapy would generally include statins (unless not tolerated), ACE inhibitors, ARBs, beta blockers, calcium channel blockers, and/or ranolazine (unless ineffective or not tolerated).
10. Able to provide signed informed consent

* Inclusion #4 was eliminated with V7 of the protocol

Exclusion Criteria

1. Myocardial infarction within 90 days prior to consent or between consent and treatment with CLBS16
2. Evidence of obstructive heart disease on screening angiogram or within 6 months prior to consent, including prior CABG at any time or history of PCI within 6 months prior to consent.
3. Planned PCI or CABG
4. Diagnosis of other specific cardiac disease including:
   a. aortic valve area < 1.0,
   b. 3+ mitral regurgitation
   c. 3+ aortic insufficiency
   d. hypertrophic cardiomyopathy
   e. suspected or diagnosed Prinzmetal angina, or if acetylcholine provocation has been performed, significant coronary spasm as defined by more than 70% reduction in vessel diameter in any vessel in response to acetylcholine
   f. severe myocardial bridging per investigator's discretion
   g. any anomalous coronary anatomy which could contribute to the subject's angina per investigator's discretion
5. LVEF < 30%
6. Glomerular filtration rate <30 mL/min/1.73m^2 (MDRD)
7. Subject currently uses coumadin, dabigatran, apixaban, rivaroxaban, or edoxaban or plans to use one of these agents during the time frame of the trial
8. Subject has serious hypersensitivity or a history of adverse reaction to G-CSF or apheresis
9. Subject has a known allergy to mouse proteins
10. Subject tests positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C
11. Subject with chronic inflammatory disease or autoimmune disease that has had an acute exacerbation of disease within the last 6 months, or subjects that are on immunosuppressive therapy or in a chronic immunosuppressive state
12. Recent history of abuse or current abuser of alcohol or recreational drugs
13. Subject is pregnant or lactating at the time of signing the consent
14. Malignant neoplasm (other than adequately treated non-melanoma skin cancer or in situ cervical carcinoma) within 5 years prior to screening
15. Subject has participated in another clinical study within 90 days prior to signing the informed consent or is scheduled to participate in another clinical study during the course of the study. Observational studies in which the subject did not receive treatment or did not undergo procedures which may compromise this study's data integrity may be allowable following Sponsor approval.
16. History of sickle cell disease
17. Previous treatment with a CD34+ cell-based therapy.

18. Any other condition which, in the opinion of the investigator, may preclude the subject from safe participation in the study or compromise data integrity

STATISTICAL ELEMENTS

Sample size justification

One hundred and five (105) subjects will be randomized in a 4:3 ratio to receive CLBS16 or placebo. Since it is a key objective to determine the effect size and variability of the clinical outcome measures, there is no formal sample size calculation for this study.

Planned Statistical Analysis

The full statistical analysis plan will be outlined in the statistical analysis plan, which will be finalized before database lock. In general, the plan will be as follows: The statistical testing will be performed between CLBS16 and placebo.

Mean change from baseline in angina frequency, ETT, CCS, and SAQ that compares the CLBS16 and placebo groups will use two sample t-test. The difference between treatment groups and confidence intervals will be estimated.

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) is defined as an AE that starts or worsens on or after G-CSF dosing and no more than 14 days after IP dosing. The number and percentage of subjects with TEAEs will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by severity and by relationship to study drug or procedures.

Change from baseline in clinical laboratory tests and vital signs will be summarized. Post-baseline electrocardiography (ECG) assessments will be summarized with respect to being normal, abnormal (not clinically significant), or abnormal (clinically significant).

The percent of subjects that have at least one MACE and the rate of MACE will be summarized. Time to first MACE or time to death will be explored using the Kaplan-Meier method. In addition to being analyzed in the safety analysis set as treated, MACE will be analyzed as randomized in the full analysis set.

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
ARB	Angiotensin receptor blocker
ASA	Acetyl salicylic acid (aspirin)
AST	Aspartate aminotransferase
BMC	Bone marrow cells
BUN	Blood urea nitrogen
BW	Body weight
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CBC	Complete blood count
CBF	Coronary blood flow
cc	Cubic centimeter
CCS	Canadian Cardiovascular Society
CEC	Clinical events classification
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
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DCM	Dilated cardiomyopathy
DMC	Data Management Committee
ECG	Electrocardiography
e-GFR	Estimated glomerular filtration rate
ETT	Exercise tolerance test
FAS	Full analysis set
FDA	Food and Drug Administration
FS	Fractional shortening

Abbreviation	Definition
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular filtration rate
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
HRQoL	Health-related quality of life
IC	Intracoronary
ICH	International Council for Harmonisation
IHD	Ischemic heart disease
IMR	Index of microvascular resistance
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board (encompasses other similar terms e.g. Independent Ethics Committee, Research Ethics Board, and Human Research Ethics Committee)
LAD	Left anterior descending
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac events
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MESA	Multi-Ethnic Study of Atherosclerosis
MET	Metabolic Equivalent of Task
MFR	Myocardial flow reserve
MPR	Myocardial perfusion reserve
MNC	Mononuclear cells
NTG	Nitroglycerin
NT-proBNP	N-terminal pro B-type natriuretic peptide
PBS	Phosphate buffered saline
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PPS	Per-protocol set
PT	Prothrombin time
QWISE	Study of Quinapril in Women with Chest Pain, Coronary Flow Reserve Limitations and Evidence of Myocardial Ischemia

Abbreviation	Definition
SAE	Severe adverse events
SAQ	Seattle Angina Questionnaire
SF-36	Short Form-36
SIC	Subject identification code
T-bil	Total bilirubin
TBV	Total blood volume
T-cho	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
TOPCARE-AMI	Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction
T-pro	Total protein
US	United States of America
WISE	Women's Ischemia Syndrome Evaluation

TABLE OF CONTENTS

TABLE OF FIGURES

1. SCHEDULE OF ASSESSMENTS

Study Procedure/ Assessment	Visit Name	Screening[a]		G-CSF Day 1	G-CSF Day 2	G-CSF Day 3	G-CSF Day 4	G-CSF Day 5	Treatment[b]					Day 1	Phone Day 8	Month 1	Month 3	Month 6	Month 12[c]
	Days	-60 to -7		-6	-5	-4	-3	-2			0			1	8	30	90	180[d]	365
	Hours								-1	0	2	4	6[e]						
	Window								before admin[f]		±15 min	±30 min	±120 min		±2 days	±4 days	±7 days	±14 days	±21 days
Informed consent[g]		X																	
Eligibility criteria		X	X						X										
Medical history and demographics		X																	
Vital signs		X		X	X	X	X	X	X	X	X	X	X	X			X	X	
12-lead electrocardiography (ECG)		X		X					X		X		X	X			X	X	
Exercise tolerance test (ETT)		X[h]																X	
Provide instructions and dispense angina and nitroglycerin diary[i]		X														X	X		X
Collect angina and nitroglycerin diary			X														X	X	X
Assess CCS angina class		X															X	X	X
Seattle Angina Questionnaire (SAQ)		X															X	X	X
Short Form-36 (SF-36)		X															X	X	X
Randomization			X																
Antiplatelet therapy			X[j]	X	X	X	X	X	X										
G-CSF administration[k]				X	X	X	X	X											

a Most screening procedures will be conducted in two or more visits. The final screening visit may be combined with G-CSF Day 1 Visit (Day -6).
b Day 0 typically occurs 1 or 2 days following manufacturing which occurs the day after apheresis is performed.
c The month 12 assessment will be by telephone/mail/email only unless the subject has a previously planned in-person care visit with the site. Diary and questionnaires will be emailed or mailed to subjects at least two weeks in advance of the scheduled assessment (or provided in-person, if applicable).
d Day 180 procedures may be performed in more than one visit, within a 7-day span.
e The 6-hour time point is optional for subjects who will be discharged prior to the 6-hour time point. An ECG is required before discharge and may be performed at the 4-hour time point.
f Hour -1 procedures can be conducted any time on the day of IP administration, prior to the start of IP administration
g Informed consent may be obtained prior to the screening window.
h If necessary, ETT can be conducted at another screening visit. However, ETT should not be conducted during the 2 weeks of angina and nitroglycerin use observation period.
i Subjects will be provided with a diary in which to make daily observations about their angina and nitroglycerin use. Subjects should complete the full 14 days of observation prior to selected visits. No other study procedures should be performed during the 14-day diary period.
j Antiplatelet therapy should be initiated before the first dose of G-CSF and continued through Treatment Day.
k The dose of G-CSF will be based on the body weight at the G-CSF Day 1 visit. Whether to administer G-CSF on day 5 is to be decided according to the results of the hematology test performed on day 5. If the white blood cell count exceeds 75,000 cells/uL on day 5, G-CSF should not be given on day 5.

Study Procedure/ Assessment	Visit Name	Screening[a]		G-CSF Day 1	G-CSF Day 2	G-CSF Day 3	G-CSF Day 4	G-CSF Day 5	Treatment[b]					Day 1	Phone Day 8	Month 1	Month 3	Month 6	Month 12[c]
	Days	-60 to -7		-6	-5	-4	-3	-2	-1	0	2	4	6[e]	1	8	30	90	180[d]	365
	Hours																		
	Window								before admin[f]		±15 min	±30 min	±120 min		±2 days	±4 days	±7 days	±14 days	±21 days
Peripheral blood draw prior to apheresis[l]								X											
Apheresis								X											
Angiogram[m]			X																
Coronary Microvascular Assessment			X[n]															X[o]	
Infusion of Investigational Product										X									
Physical exam		X							X[p]								X[p]	X[p]	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and non-drug therapies		X	X	X	X	X	X	X	X					X	X	X	X	X	X
Hematology		X						X[q]	X					X		X		X	
Coagulation factors[r]		X												X				X	
Clinical chemistry panel		X							X					X		X		X	
Troponin[s]									X			X		X					
Lipid panel		X																X	
Urinalysis		X																	
Serology[t]		X																	
Pregnancy test (dip-stick)		X		X					X								X	X	

l Includes collection of 100 mL of peripheral blood to be sent to Cognate, as well as an optional CD34+ count resulted locally to guide apheresis parameters.
m If an angiogram to exclude obstructive disease has not been performed within 6 months prior to screening, it may be performed during the screening period.
n May occur within 180 days prior to consent.
o Coronary microvascular assessment at Month 6 is optional. If performed, it must use the same methodology as that for the baseline assessment.
p Targeted physical exam
q The hematology assessment will be performed locally on G-CSF Day 5. Additionally, on G-CSF Day 5, prior to apheresis, a blood sample may be taken for a local CD34+ cell count to guide apheresis parameters.
r Coagulation factors to consist of PT, APTT, and INR.
s Troponin assessments should be made by local laboratory using the institution's preferred assay method. The same assay method should be used at each time point. Clinically significant increases in troponin from pre-infusion values must be reported as an adverse event.
t Serology includes: HIV, hepatitis B, and hepatitis C. If drawn > 29 days prior to the G-CSF Day 5 visit, a repeat serology sample must be drawn. See Central Lab Manual for full details.

2. BACKGROUND AND SIGNIFICANCE

2.1 Coronary Microvascular Dysfunction

Subjects with symptoms, evidence of ischemia, and no obstructive coronary artery disease (CAD) are prevalent and increasing in frequency.[1] The prevalence of nonobstructive CAD at coronary angiography amongst subjects presenting with chest pain is 20% to 30%[2, 3] and has been reported to be up to 50%.[4] Such subjects have disability, healthcare resource consumption, and costs similar to those with obstructive CAD.[5, 6] Functional coronary microvascular abnormalities mediate ischemia and cause angina[7, 8] and have been linked to adverse clinical outcomes.[9, 10] Thus, coronary microvascular dysfunction (CMD) may serve as the underlying mechanism for the symptoms and cardiovascular events observed in subjects with nonobstructive ischemic heart disease (IHD).

In a recent study of subjects 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 subjects had evidence of CMD.[11] Considerable data document that CMD contributes to myocardial perfusion abnormalities in regions supplied by vessels without epicardial stenosis[12-14] in subjects with risk factors and/or angina, but without epicardial stenosis.[15-18] It is now evident that CMD is not benign and is predictive of adverse cardiovascular outcomes. In the Multi-Ethnic Study of Atherosclerosis (MESA), both myocardial flow (cardiac magnetic resonance imaging [cMRI]) during adenosine-induced hyperemia and flow reserve were inversely associated with risk factor burden.[19] CMD has been documented among symptomatic women without flow-limiting coronary stenosis in the Women's Ischemia Syndrome Evaluation (WISE)[20, 21] study by directly measured (Doppler flow wire) coronary flow, by cMRI,[22] and by positron emission tomography (PET).[9] These studies have linked CMD and atherosclerosis risk factors with adverse outcomes over follow-up. CMD has also been documented in another female cohort,[23] providing additional support for its link with several risk factors.

2.2 CD34+ Cell Therapy

The potential role of autologous CD34+ cells for the treatment of CMD has recently been demonstrated by the ESCAPE CMD trial.[24, 25] In that trial, statistically significant improvement in coronary flow reserve (CFR) was observed, along with statistically significant reduction in Canadian Cardiovascular Society (CCS) angina class and angina frequency, and statistically significant improvements in quality of life.

The potential role of autologous CD34+ cells for the treatment of CMD is further 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 subjects with reperfused acute myocardial infarction (AMI). Intracoronary infusion of bone marrow cells (BMCs; rich in CD34+ cells) in subjects 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. Subsequently the salutary effects of BMCs were shown to be statistically driven by the SDF-1 migratory function of the administered cells.[26] Since CD34 cells are the primary cells in the bone marrow that express the CXCR4 receptor, these findings provide further support for the ability of CD34 cells to enhance microvascular function. 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 subjects with AMI.[27] These results are supported by the Transplantation of Progenitor Cells and Regeneration Enhancement in AMI (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 subjects with successfully reperfused AMI.[28]

Thus, 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. Further exploration of the treatment of CMD with CD34+ cells will be an important next step towards making this therapy more broadly available.

2.3 Findings from Nonclinical Studies

2.3.1 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 granulocyte-colony stimulating factor (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.

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

Analysis of the efficacy data revealed a statistically significant improvement in both fractional shortening (FS) (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 x 10^5 CD34+ cells/kg when compared to animals in the PBS group, respectively. A statistically significant improvement was also noted in 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 x 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 x 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 CD34+ cells are safe and efficacious for myocardial ischemia treatment in the rat model.

2.4 Findings from Clinical Studies

2.4.1 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 subjects with no-option refractory angina evaluating 2 doses (1x10^5 or 5x10^5 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 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 subjects 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 subjects than in placebo-treated subjects (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 subjects 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 subjects. 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.

2.4.2 **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 subjects with nonischemic dilated cardiomyopathy (DCM).[30] Of 110 subjects with DCM, 55 were randomized to CD34+ cell transplantation (SC group) and 55 subjects did not receive stem cell therapy (Controls). In the SC group, peripheral blood CD34+ cells were mobilized by G-CSF and collected via apheresis. Subjects 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 left ventricular ejection fraction (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%) subjects 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 subjects 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 subjects 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 subjects with ischemic cardiomyopathy in a prospective phase 1 crossover study (NCT01350310).[31] A total of 33 subjects with ischemic cardiomyopathy and New York Heart Association class III and LVEF <40% were enrolled. In phase 1, subjects were treated with medical therapy for 6 months. Thereafter, all subjects underwent intramyocardial CD34+ cell transplantation. Peripheral blood CD34+ cells were mobilized by G-CSF, collected via apheresis, and injected intramyocardially in the areas of hibernating myocardium. Subjects were followed for 6 months after the procedure (phase 2). Two subjects died during phase 1 and none during phase 2. The remaining 31 subjects were 85% men, aged 57±6 years. In phase 1, there was no change in LVEF (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 LVEF (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 subjects with ischemic cardiomyopathy.

2.4.3 Proof of Concept Study of CLBS16 in Subjects with Coronary Microvascular Dysfunction

Protocol CLBS16-P01 was a proof-of-concept study conducted with CLBS16.[24, 25] The population studied is similar to the population in this protocol.

Men and women 18 years of age and older without obstructive disease on coronary angiogram within 6 months prior to screening and no obstructive coronary artery disease as defined by lesion stenosis < 50% in any artery as visualized by diagnostic angiography were studied. Patients who had a history of effort-induced anginal symptoms and currently experience angina were eligible for the study. Patients with prior evidence of obstructive heart disease, history of coronary artery bypass graft (CABG) or percutaneous intervention (PCI) or diagnosis of specific cardiac disease such as severe valvular heart disease were excluded from the study. Patients experiencing a myocardial infarction within 90 days prior to consent or between consent and treatment with CLBS16 or with a LVEF < 40% were excluded.

The main endpoint of the study was CFR at 6 months after administration of CLBS16. CFR results are shown in **Figure 1**. A statistically significant increase in CFR was observed.

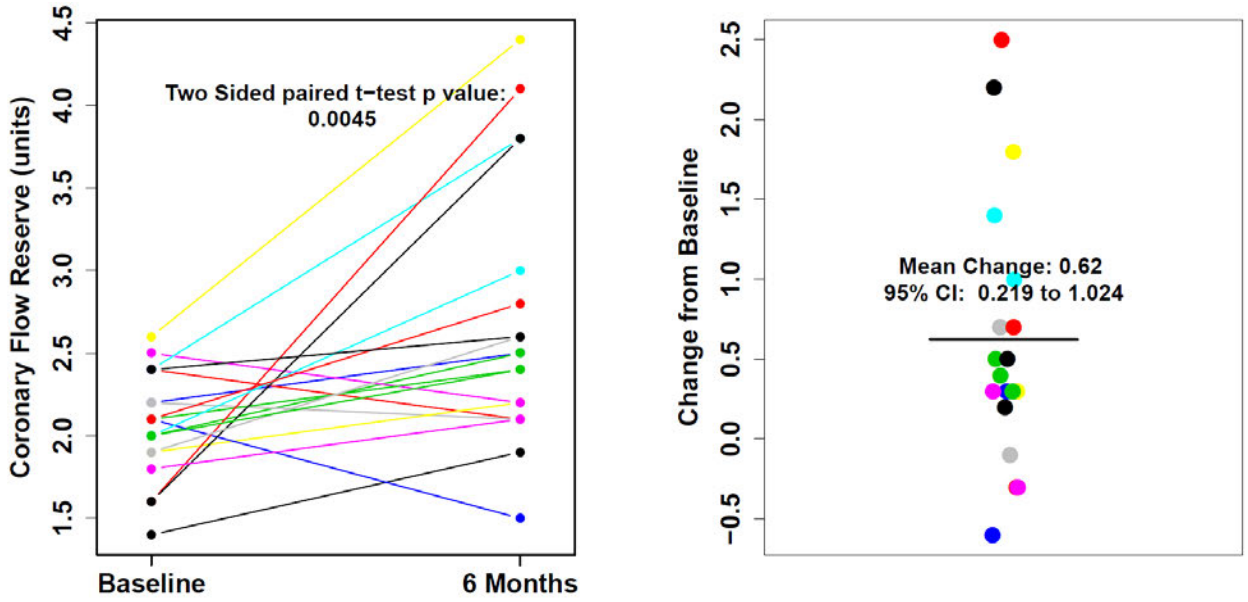

Figure 1. Coronary Flow Reserve in Subjects with CMD Prior to and 6-Months Following Treatment with CLBS16

CCS angina class (**Figure 2**) and angina frequency (**Figure 3**) were also significantly improved and the Seattle Angina Questionnaire indicated significant improvements in all categories (**Figure 4**).

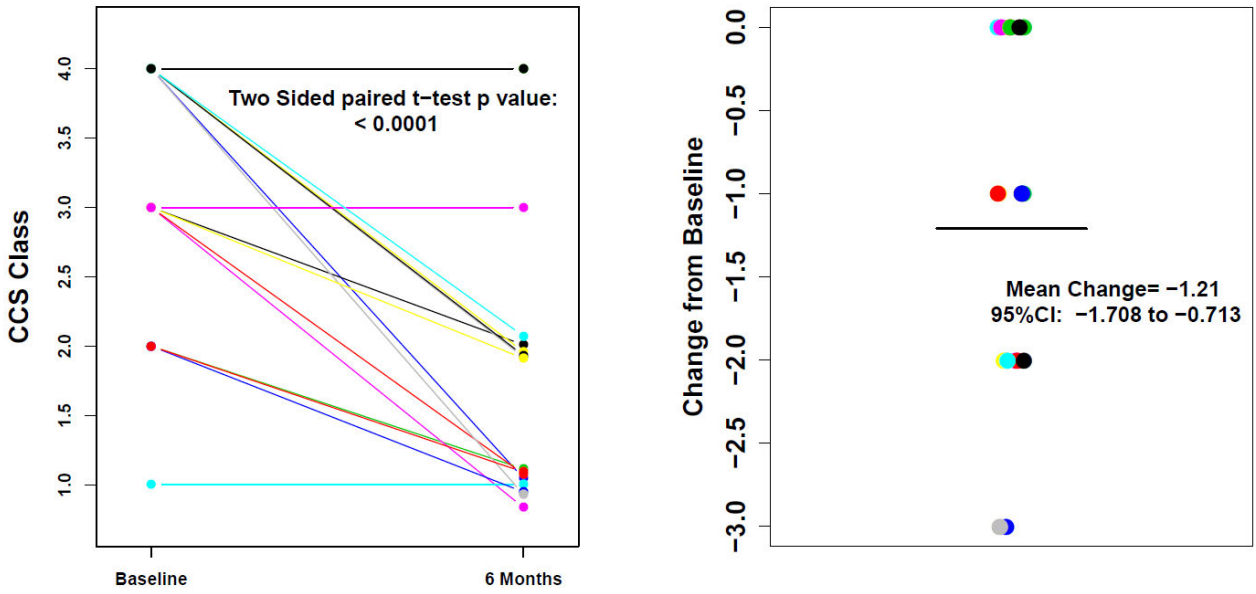

Figure 2. CCS Angina Class in Subjects with CMD Prior to and 6-Months Following Treatment with CLBS16.

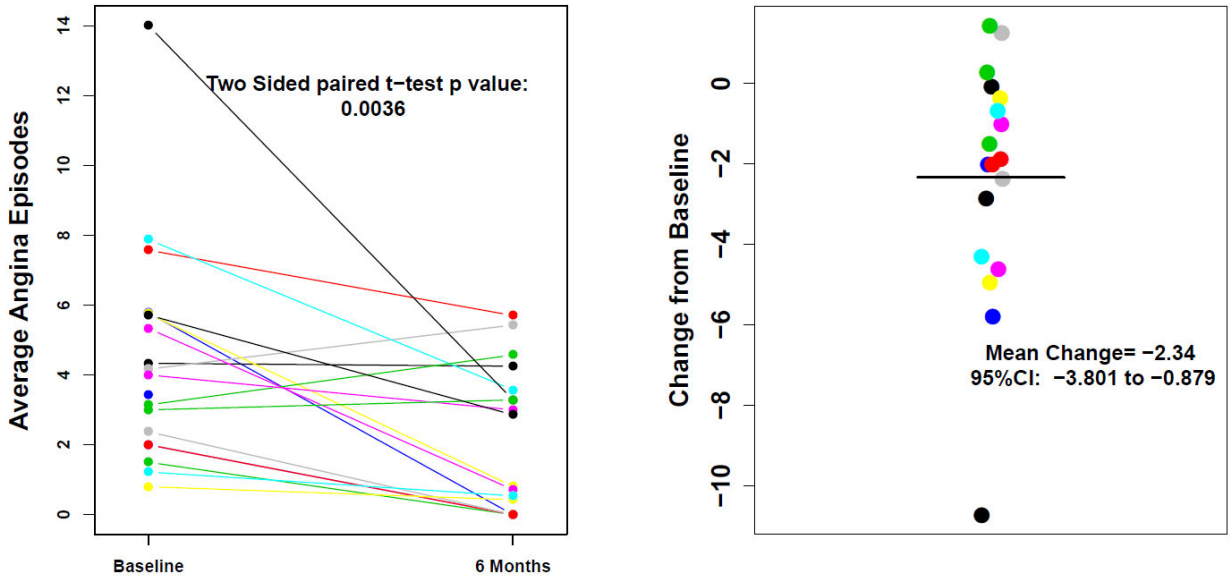

Figure 3. Angina Frequency in Subjects with CMD Prior to and 6-Months Following Treatment with CLBS16.

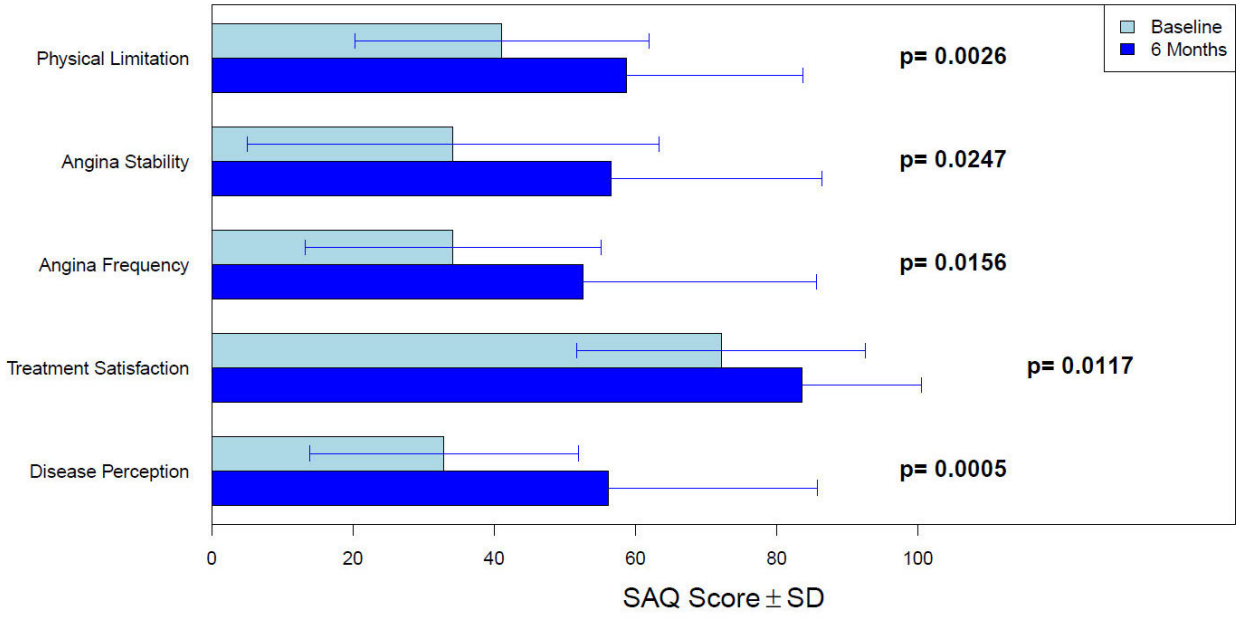

Figure 4. Seattle Angina Questionnaire Assessment in Subjects with CMD Prior to and 6-Months Following Treatment with CLBS16.

2.5 Description of Investigational Product

The investigational product (IP) consists of 1 x 10^6 to 300 x 10^6 autologous CD34+ cells.

Autologous CD34+ cells will be suspended in an isotonic solution with autologous serum and human serum albumin. Placebo will consist of the identical diluent solution without the cells (i.e., an isotonic solution with autologous serum and human serum albumin).

3. STUDY OBJECTIVES

3.1 Efficacy Objectives

To evaluate the effect size and variability of CLBS16 in subjects with CMD and without obstructive coronary artery disease on angina frequency, exercise tolerance test (ETT), Canadian Cardiovascular Society (CCS) angina classification, and quality of life.

3.2 Safety Objectives

To evaluate the safety of CLBS16 in subjects with CMD and without obstructive CAD.

4. STUDY DESIGN

This is a phase 2 randomized, double-blind, and placebo-controlled clinical study to evaluate the efficacy and safety of CLBS16 in subjects with CMD and without obstructive coronary artery disease. The study will be conducted in the phases as outlined below:

4.1 Screening Phase

Subjects who provide informed consent will be screened for eligibility within 60 days before beginning the study treatment phase. All subjects must have a diagnosis of CMD based on a coronary microvascular assessment as outlined in Section 6. Briefly, a diagnosis of CMD can be based on any of the following thresholds: coronary flow reserve (CFR) ≤2.5, coronary blood flow (CBF) response to acetylcholine ≤50%, myocardial perfusion reserve (MPR) or myocardial flow reserve (MFR) <2.0, or index of microvascular resistance (IMR) > 25. A coronary microvascular assessment prior to the study is allowed if it occurred within 180 days prior to the first screening visit. Any cardiovascular medical therapy must be at a stable dose for at least 30 days prior to the first screening visit and must be maintained at that dose throughout the duration of the study; cardiovascular therapy would generally include statins (unless not tolerated), angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB)s,

beta blockers, calcium channel blockers, and/or ranolazine (unless ineffective or not tolerated). Baseline angina and nitroglycerin diary, Health Related Quality of Life (HRQoL), and ETT will also be assessed.

Approximately 105 eligible subjects will be randomized to receive CLBS16 or placebo in a 4:3 ratio.

4.2 G-CSF and Treatment Phase

All research subjects will receive subcutaneous injections of G-CSF at a dose of 5 µg/kg/day for 5 days to mobilize CD34+ cells into the peripheral blood. White blood cell counts in peripheral blood will be assessed on G-CSF Day 5 prior to administration of G-CSF, and if the white blood cell count exceeds 75,000 cells/µL, that day's G-CSF will not be given.

On G-CSF Day 5, just prior to apheresis, peripheral blood will be collected, which will be used for processing autologous serum, to be used in formulating the IP. Subjects will then undergo apheresis to collect CD34+ cells. CD34+ cells will be isolated using the CliniMACS System (Miltenyi Biotec).

CD34+ cells (CLBS16) or placebo will be delivered via IC administration (Section 18.4). Non-heparin anticoagulant will be administered to achieve an active clotting time (ACT) of >200 seconds during the procedure. The catheter will be positioned in the midportion of the target artery. The catheter will be primed. The total product volume will be administered at a rate of 1.0 mL/min.

4.3 Observation Phase

All efficacy assessments will be performed through 6 months after treatment to evaluate the potential bioactivity of CLBS16 or placebo in subjects with coronary microvascular dysfunction. Select efficacy assessments which may not require an in-person visit (angina frequency, nitroglycerin use, CCS angina class, SAQ, and SF-36) will also be collected at 12 months.

At the discretion of the investigator, assessment of coronary microvascular function may be performed at 6 months after administration of CLBS16 or placebo. If this assessment is performed, it should be with the same methodology used for this assessment at baseline.

The occurrence of AEs, SAEs, and MACE will be collected for all subjects from the time of signing consent through the 6-month follow-up period to evaluate the safety and

tolerability of CLBS16 or placebo. AEs will also be collected for subjects who undergo an assessment at 12 months.

4.4 Rationale for Duration of Subject Participation

Subjects will be followed for up to 12 months after receiving treatment, extending the observation time from the previous phase 2 study, CLBS16-P01 (NCT03508609

4.5 Randomization and Blinding

Subjects will be randomized to receive CLBS16 or placebo. A randomization schedule will be generated prior to the start of the study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

All study subjects and study site personnel will be blinded with regard to active versus placebo treatment assignments for the duration of the study.

The investigational product blind shall not be broken during the observation period by the investigator unless in emergency cases. As this is a one-time intervention in which subjects in the CLBS16 treatment and placebo control arms will both undergo G-CSF cell mobilization, apheresis, and IC infusion, circumstances that might require unblinding are not foreseen. If the investigator feels that the treatment group assignment must be known due to serious and life-threatening issues, the investigator must contact the Sponsor's primary medical monitor and if not available, the Sponsor's study manager on how to proceed. The investigator must keep a deviation log stating the date and time of breaking the code, reason for breaking the code, IP administered, subject identification number and randomization code, person who requested and performed the unblinding, and site personnel who were unblinded. Additional follow-up to assess the ongoing status of the subject will be performed. A written explanation of the reasons for unblinding will be provided by the investigator. All deviation logs will be collected by the Sponsor at the end of the study.

4.6 Stopping Rules

4.6.1 Stopping for Individual Subjects

Treatment of an individual subject should not be undertaken if any issue is identified which would create an unreasonable risk for administration of CLBS16. Treatment should also not be undertaken if any issue is identified which would create an unreasonable risk for any assessments required by the protocol. Any such decision may be made prior to initiation of the treatment procedure or at any point during a

microvascular testing or investigational product administration procedure. Investigators may abort the treatment procedure if any event(s) occurs that in their expert medial opinion represents an additive risk to the subject for continuation of the infusion.

Once treated with investigational product, a subject should be followed for all safety and efficacy measures outlined in the protocol, to the extent possible. However, efficacy measures such as coronary microvascular assessment should not be undertaken if any issue is identified which would create an unreasonable risk for the subject.

4.6.2 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. Observation and collection of safety data for all subjects already treated should continue to the extent possible.

An independent data monitoring committee (DMC) will play an active role in monitoring the study and full guidelines are delineated in the DMC charter. At any time, the DMC may make recommendations to the Sponsor as to whether or not the study should continue, be modified or discontinue.

The frequency and timing of DMC meetings will be finalized by the DMC prior to or near the enrollment of the first subject, as described in the DMC charter. Ad hoc DMC meetings will be held if any of the following safety thresholds are observed in the peri-procedural / treatment period after the first 20 subjects:

- >15% cumulative MACE
- >5% cumulative incidence of death, or severe stroke
- >10% myocardial infarction

5. STUDY ENDPOINTS

5.1 Efficacy Endpoints

- Change from baseline in angina frequency at 3, 6, and 12 months captured by angina diary
- Change from baseline in CCS angina class at 3, 6, and 12 months
- Change from baseline in total exercise time and peak metabolic equivalent of task (MET) as measured by ETT using the modified Bruce protocol at 6-months

- Change from baseline in HRQoL as measured by the Seattle Angina Questionnaire (SAQ) and Short Form-36 (SF-36) at 3, 6, and 12 months
- Proportion of subjects with ETT-induced angina at 6 months
- Proportion of subjects with ETT-induced ST-segment changes at 6 months
- Change from baseline in nitroglycerin use at 3, 6, and 12 months

5.2 Safety Endpoints

- AEs, including SAEs
- Laboratory investigations
- Physical examinations
- Vital signs
- MACE
- Death

5.3 Exploratory Endpoints

- Change from baseline in time to onset of angina and time to ST segment changes during ETT
- Change from baseline in CFR at 6 months in a subset of subjects
- Change from baseline in MPR or MFR at 6 months in a subset of subjects
- Change from baseline in IMR at 6 months in a subset of subjects
- Change from baseline in CBF at 6 months in a subset of subjects

6. STUDY POPULATION

Men and women 18 years of age and older, with CCS class II, III, or IV and without obstructive disease on coronary angiogram within 6 months prior to or during screening will be studied. Subjects must also have a diagnosis of CMD. Allowable methods for assessing coronary microvascular function and associated thresholds are shown in Table 1. Subjects who have a history of effort-induced anginal symptoms and currently experience angina will be eligible for the study. Subjects with any prior history of coronary artery bypass graft (CABG), evidence of obstructive heart disease, percutaneous intervention (PCI) (within 6 months prior to consent) or diagnosis of specific cardiac disease such as severe valvular heart disease will be excluded from the study. Subjects experiencing a myocardial infarction within 90 days prior to consent or between consent and treatment with CLBS16 or with a left ventricular ejection fraction (LVEF) < 30% will be excluded. See below for a detailed description of the subject eligibility criteria.

Table 1. Allowable Methods for Assessing Coronary Microvascular Function and Associated Thresholds

Method	Threshold
Coronary flow reserve by Doppler wire (d-CFR)[20, 21, 32]	≤2.5
Coronary flow reserve by thermodilution (t-CFR)[33, 34]	≤2.5
Change in coronary blood flow (CBF) to acetylcholine challenge[11]	≤50%
MPR or MFR by positron emission tomography (PET)[9, 35-37]	<2.0
MPR or MFR by cardiac magnetic resonance imaging (cMRI)[38-40]	<2.0
Index of Microcirculatory Resistance (IMR)[33, 41, 42]	>25

6.1 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, despite maximally tolerated doses of antianginal medications, statins, ACE inhibitors, angiotensin receptor blockers (ARBs) and other medications thought to positively impact subjects with CMD.
3. Diagnosis of CMD based on the following physiological assessments: coronary flow reserve (CFR) ≤2.5, coronary blood flow (CBF) response to acetylcholine ≤50%, myocardial perfusion reserve (MPR) or myocardial flow reserve (MFR) <2.0, or index of microvascular resistance > 25. Physiologic assessments within 180 days prior to or during the screening period are accepted.
4. †
5. CCS class II, III, or IV chronic refractory angina as evaluated by the site
6. No obstructive disease on coronary angiogram within 6 months prior to or during screening. The following is allowed: a coronary artery stenosis less than 40% in the left main coronary artery, or a stenosis less than 50% in any other epicardial coronary artery.
7. If subject is of childbearing potential, the subject must have a negative pregnancy test at screening and prior to mobilization and G-CSF treatment, and prior to

† Inclusion #4 was eliminated with V7 of the protocol

receiving treatment. The subject agrees to employ adequate birth control measures for the duration of the study. Acceptable methods of birth control are: oral contraceptive tablets, hormonal implant device, hormonal patch, intrauterine device, diaphragm and contraceptive cream or foam, condom with spermicide, partner vasectomy, or abstinence.

8. Subject is willing and able to comply with the requirements of the protocol
9. Any cardiovascular medical therapy must be at a stable dose for at least 30 days prior to the first screening visit and must be maintained at that dose throughout the duration of the study; cardiovascular therapy would generally include statins (unless not tolerated) ACE inhibitors, ARBs, beta blockers, calcium channel blockers, and/or ranolazine (unless ineffective or not tolerated).
10. Able to provide signed informed consent

6.2 Exclusion Criteria

1. Myocardial infarction within 90 days prior to consent or between consent and treatment with CLBS16
2. Evidence of obstructive heart disease on screening angiogram or within 6 months prior to consent, including prior CABG at any time or history of PCI within 6 months prior to consent
3. Planned PCI or CABG
4. Diagnosis of other specific cardiac disease including:
   a. aortic valve area < 1.0,
   b. 3+ mitral regurgitation
   c. 3+ aortic insufficiency
   d. hypertrophic cardiomyopathy
   e. suspected or diagnosed Prinzmetal angina, or if acetylcholine provocation has been performed, significant coronary spasm as defined by more than 70% reduction in vessel diameter in any vessel in response to acetylcholine
   f. severe myocardial bridging per investigator's discretion
   g. any anomalous coronary anatomy which could contribute to the subject's angina per investigator's discretion
5. LVEF < 30%
6. Glomerular filtration rate <30 mL/min/1.73m^2 (MDRD)
7. Subject currently uses coumadin, dabigatran, apixaban, rivaroxaban, or edoxaban or plans to use one of these agents during the time frame of the trial
8. Subject has serious hypersensitivity or a history of adverse reaction to G-CSF or apheresis
9. Subject has a known allergy to mouse proteins

10. Subject tests positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C
11. Subject with chronic inflammatory disease or autoimmune disease that has had an acute exacerbation of disease within the last 6 months, or subjects that are on immunosuppressive therapy or in a chronic immunosuppressive state
12. Recent history of abuse or current abuser of alcohol or recreational drugs
13. Subject is pregnant or lactating at the time of signing the consent
14. Malignant neoplasm (other than adequately treated non-melanoma skin cancer or in situ cervical carcinoma) within 5 years prior to screening
15. Subject has participated in another clinical study within 90 days prior to signing the informed consent or is scheduled to participate in another clinical study during the course of the study. Observational studies in which the subject did not receive treatment or did not undergo procedures which may compromise this study's data integrity may be allowable following Sponsor approval.
16. History of sickle cell disease
17. Previous treatment with a CD34+ cell-based therapy.
18. Any other condition which, in the opinion of the investigator, may preclude the subject from safe participation in the study or compromise data integrity

7. INVESTIGATIONAL PRODUCT

7.1 Mobilization of CD34+ cells from bone marrow with G-CSF

[redacted]

7.2 Apheresis Procedure for Harvesting CD34+ Cells from Peripheral Blood

[redacted]

7.3 Description of Treatment

[redacted]

This dose level was used in study CLBS16-P01 and was successful in providing a favorable efficacy outcome with no cell-related adverse events.[24, 25] Further support comes from three previous clinical studies which demonstrated efficacy and safety from intracoronary administration of CD34+ cells. 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 subjects with nonischemic dilated cardiomyopathy.[44] 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 subjects with intractable angina.[45] 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 subject. 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 subjects 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 subject. 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.

With coronary infusions, there are two approaches that have been used, one approach being to use a balloon-based stop-flow technique and the other to administer the infusion without stopping the blood flow. A study performed by Musialek and colleagues compared these methods with intracoronary administration and found that administration without stopping the flow to be comparable in terms of delivery of cells into myocardial tissue, but was better tolerated.[46] Thus, for this study, IC infusion without stopping blood flow (i.e. without inflating balloon) was chosen.

7.4 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. 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.

7.5 Packaging, Labeling, and Storage

[redacted] A label will include subject identifiers, product expiration date and 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 biohazard bag and placed in a secure transportation box (temperature maintained at 2-10 °C) to be delivered to the cardiac catheterization facility, typically the day after completion of manufacturing of the CLBS16 product. Additional details can be found in the investigational product manual.

Within 4 hours prior to injection, the site will open the shipping container containing CLBS16 and record time of unpacking. The temperature reading from the temperature recording device will be recorded. If the temperature reading is outside of the 2-10º C range, site personnel must contact Caladrius to determine whether the investigational product can be administered and temperature deviation information must be documented. CLBS16 or placebo can remain at ambient temperature for up to 4 hours prior to administration; however, if there will be a delay of more than 4 hours before administration of the IP, please contact the Sponsor for storage and administration instructions.

7.6 Administration

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

The CLBS16 or placebo infusion procedures are outlined in Section 18.4; detailed procedures are provided in the investigational product manual. The catheterization laboratory report (with event log) for the infusion procedure should be provided to Caladrius medical monitor within 24 hours (see PERSONNEL AND FACILITIES).

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

7.7 Completion of IP product release testing

Prior to the manufacturer's authorization of the IP for administration, preliminary release testing will have been completed. However, due to the short shelf-life of the IP and the extended time required to complete final safety testing, final testing results will not be available until after IP administration has completed. If final safety results are negative, the PI and site will not be notified. If positive results are obtained after IP administration, the PI will be notified immediately. Additionally, regulatory authorities and IRB will be notified if applicable. Local infectious disease specialists could be consulted, and anti-microbial therapy will be considered for the subject as deemed appropriate by the Investigator.

7.8 Procedure for unblinding

Unblinding is generally not necessary during the observation period, even in the event of an adverse event, unless knowledge of the treatment code would influence treatment decisions. If knowledge of the treatment code is thought to influence treatment decision, unblinding can be achieved through the same system used for patient randomization (see study manual).

8. STUDY VISIT ASSESSMENTS

Additional details on study procedures can be found in Section 1, Schedule of Assessments, Section 10, Assessments of Efficacy, and in Section 18, Supplements.

8.1 Screening Visits (Day -60 to -7)

There will be two or more screening visits, which should be at least 14 days apart in order to be able to collect two weeks' worth of angina/nitroglycerin diary data. The final Screening Visit may be combined with G-CSF Day 1 visit.

At the first screening visit, perform the following:

- Administer informed consent
- Review inclusion and exclusion criteria to determine study eligibility
- Collect medical history including demographics (i.e. sex, date of birth, race, and ethnicity)
- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Perform physical examination

- Assess CCS angina classification
- Administer the SF-36 Questionnaire
- Administer Seattle Angina Questionnaire
- Collect vital signs
- Collect blood for hematology and clinical chemistry
- Collect blood for lipid panel
- Collect blood for coagulation factors
- Collect urine for urinalysis
- Collect blood for serology (HIV, hepatitis b, and hepatitis c). Serology testing must occur within 29 days of apheresis.
- Perform urine pregnancy test on female subjects of childbearing potential
- Perform 12-lead ECG
- Perform ETT
- Dispense and provide instructions for angina and nitroglycerin use diary

At the second screening visit, perform the following:

- Perform coronary microvascular assessment if not available from an assessment performed within 180 days prior to the first screening visit; may be performed on a different day if needed
- Angiogram to exclude obstructive disease can also be performed, if not available within 6 months prior to the first screening visit
- Collect angina and nitroglycerin use diary
- Assess for adverse events
- Collect information on concomitant medications (including non-drug therapies)
- Review inclusion and exclusion criteria to confirm study eligibility
- Randomize the subject
- If appropriate, dispense antiplatelet medication(s) for subject to begin taking before first administration of G-CSF

8.2 **G-CSF Visits (Days -6, -5, -4, -3, and -2)**

The following will be performed or assessed at each of the G-CSF administration visit days unless noted:

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

- Perform urine pregnancy test on female subjects of childbearing potential (only on G-CSF Day 1)
- Perform 12-lead ECG (only on G-CSF Day 1)
- Collect blood for hematology (local lab; Day 5 only)
- Administer G-CSF
- On G-CSF Day 5, a blood sample may be collected for assessment of CD34+ cells in peripheral blood
- On G-CSF Day 5, just prior to apheresis, collect peripheral blood for processing autologous serum
- Perform apheresis (only on G-CSF Day 5)

8.3 Treatment Visit (Day 0)

8.3.1 Pre-infusion of IP (*any time during the day 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
- Collect blood for troponin (local laboratory)
- Perform urine pregnancy test on female subjects of childbearing potential
- Perform vital signs
- Perform 12-lead ECG
- Confirm eligibility criteria prior to IP infusion

8.3.2 IP infusion

- Perform vital signs just prior to infusion (blood pressure and heart rate only)
- Perform infusion of IP (see Section 18.4 and investigational product manual)
- Assess for adverse events

8.3.3 Post-infusion of IP (*Time 2, 4, and 6 hours*)

The following will be performed or assessed 2 (±15 min), 4 (±30 min), and 6 (±120 min) hours post IP infusion:

- Perform vital signs (blood pressure and heart rate only)
- Perform 12-lead ECG (only at the 2- and 6-hour time points)
- Collect blood for troponin at the 4-hour time point (local laboratory)

- Assess for adverse events
- The 6-hour time point is optional for subjects who will be discharged prior to the 6-hour time point. An ECG is required before discharge and may be performed at the 4-hour time point.
- If the IP infusion occurred late in the day whereby the 4- and 6- hour time point assessments would not be possible in the catheterization outpatient recovery unit, the subject may be kept overnight in the hospital to complete these assessments. Note: If the subject has any evidence of an adverse event (during or post-procedure) which is considered when deciding to hospitalize the patient overnight, this should be captured and reported as an SAE

8.4 **Day 1 visit**

- Collect information on concomitant medications (including non-drug therapies)
- Perform vital signs (blood pressure and heart rate only)
- Perform 12-lead ECG
- Collect blood for hematology and clinical chemistry
- Collect blood for troponin (local laboratory)
- Collect blood for coagulation factors
- Assess for adverse events

8.5 **Day 8 visit (Phone call)**

The subject will receive a phone call from the investigative site to 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

8.6 **Day 30 visit**

- Collect information on concomitant medications (including non-drug therapies)
- Collect blood for hematology and clinical chemistry
- Assess for adverse events
- Provide instructions and dispense angina and nitroglycerin diary

8.7 **Day 90 visit**

- Administer SF-36 Questionnaire
- Administer Seattle Angina Questionnaire

- Assess CCS angina classification
- Collect angina and nitroglycerin use diary
- Provide instructions and dispense angina and nitroglycerin diary
- Collect information on concomitant medications (including non-drug therapies)
- Assess for adverse events
- Perform 12-lead ECG
- Perform vital signs
- Perform targeted physical exam
- Perform pregnancy test on females of childbearing potential

8.8 **Day 180 visit**

Note that the day 180 procedures may be performed across more than one visit day, within a span of 7 days.

- Administer SF-36 Questionnaire
- Administer Seattle Angina Questionnaire
- Assess CCS angina classification
- Collect angina and nitroglycerin use diary
- 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
- Collect blood for coagulation factors
- Perform targeted physical exam
- Perform ETT
- Perform optional coronary microvascular assessment per discretion of the investigator (see Coronary Microvascular Assessment Manual)
- Perform pregnancy test on females of childbearing potential

8.9 **Day 365 visit (phone call)**

The Day 365 procedures will be performed by telephone, email, and mail and may occur over several days or weeks. The following procedures will be performed:

- Administer SF-36 Questionnaire
- Administer Seattle Angina Questionnaire

- Assess CCS angina classification
- Collect angina and nitroglycerin use diary
- Collect information on concomitant medications (including non-drug therapies)
- Assess for cardiac-related adverse events

8.10 Early Termination Visit

In the event of early termination prior to Day 180, perform the assessments for the Day 180 visit, if possible, with the following exceptions:

- Labs do not need to be collected again if they have been collected in the past 30 days
- Treadmill testing does not need to be performed if it was performed within the past 60 days
- Coronary microvascular assessment, if elected, should not be performed if it was performed within the past 90 days

In the event of early termination after Day 180, perform the assessments for the Day 365 visit, if possible.

9. SUBJECT MANAGEMENT

9.1 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.

9.2 Subject Identification Code (SIC)

The following series of numbers will comprise the SIC: 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 002-003. All study documents (e.g., clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the SIC.

9.3 Screening

Subjects must provide informed consent and meet all inclusion/exclusion criteria and have screening procedures performed within the screening window (-60 to -7 days).

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.

9.4 Randomization

Subjects will be randomized according to a randomization scheme generated before initiation of the study. Details of randomization procedures will be provided in the study manual.

9.5 Study Visits

Details on the procedures to be performed at each study visit, including screening, can be found in Section 1. Detail of procedures performed at each study visit can be found in Section 8.

9.6 Recording of Medications and Non-Drug Therapies

Beginning from the time of consent, all medications actively being taken (i.e., not including “as needed” or PRN medications that are not actually taken during study participation) and non-drug therapies received and all concomitant medications taken or administered during the study will be documented in the subject’s study records.

9.7 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.

9.8 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.

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. A subject will be withdrawn from the study for any of the following reasons:

- lost to follow-up
- withdraw of consent
- death

Subjects may withdraw from the study at any time and for any reason. 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.

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.

10. ASSESSMENTS OF EFFICACY

Note that the efficacy assessments during subject visits should generally be conducted in the order listed here, i.e. questionnaires and collection of information from the subject should be done at the beginning, physical exams and labs should be next, and ETT and coronary microvascular assessment should be conducted last.

10.1 Coronary Microvascular Assessment

An assessment of microvascular function is core to the diagnosis of CMD. Several invasive and non-invasive methods have been validated for diagnosis of CMD and are in current use.[33, 47-59] These methods include invasive CFR assessed by Doppler wire or thermodilution, invasive assessment of IMR, invasive assessment of CBF, and non-invasive assessment of MPR or MFR by PET or MRI as outlined in Table 1.

Further discussion of the allowable coronary microvascular assessment procedures are found in the Coronary Microvascular Assessment Manual.

10.2 Angina and Nitroglycerin Diary

Subjects will be provided with a diary in which to make daily observations about their angina and nitroglycerin use during the 2-week period prior to selected visits. Subjects should complete the full 14 days of observation prior to selected visits. The diary can be found in Section 18.1.

Note that angina which is substantially worse at Day 90 or Day 180 versus baseline should be considered for reporting as an adverse event.

10.3 CCS Angina Classification

CCS angina classification will be graded by the PI (or designee) at baseline and Day 180 according to the system developed by Campeau.[60, 61] The classification system is shown in **Table 2**.

Table 2. Canadian Cardiovascular Society Grading of Angina Pectoris

Grade	Description
Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

10.4 Short Form 36 Questionnaire

The SF-36 is a validated health survey questionnaire that will be used to measure over all functional health and well-being of participating subjects. The SF-36 can either be self-administered or administered by a trained study staff. The 36 questions will yield an 8-scale profile that will evaluate the relative burden of disease and health benefits of the treatment. A copy of the SF-36 Questionnaire is provided in Section 18.3.

10.5 Seattle Angina Questionnaire

Angina frequency and disease perception/quality of life will be assessed using the full version of the Seattle Angina Questionnaire (SAQ).[62] The SAQ will be administered at screening, and at the 90 and 180-day visits. Details of the SAQ can be found in Section 18.2.

10.6 Exercise Tolerance Test

Exercise tolerance will be assessed on a treadmill using the modified Bruce protocol.[63] Subjects should be on a stable medical regime for at least 30 days prior to the baseline ETT and not change their medications throughout the course of the study. Each subsequent test should be scheduled within 1.5 hours of the previous test. Briefly, exercise is performed on a treadmill. The ECG are placed on the chest wall. The treadmill is started at 2.7 km/hr (1.7 mph) and at a gradient (or incline) of 0%. At three-minute intervals the incline of the treadmill and speed increase as shown in Table 3. The test is generally stopped when the subject is unable to continue due to discomfort or fatigue, but other reasons are detailed in the ETT manual. The primary metrics for the test are the amount of time in seconds for which the subject is able to continue with the test and the peak METs at the time the subject stops exercising. An ETT core laboratory will provide central reading of ETTs, including the time to ST segment depression or elevation from EKG tracings.

Table 3. Stages and gradients for the Modified Bruce Protocol ETT.

Stage	Minutes	Speed (km/hr)	Speed (mph)	Gradient
0	3	2.7	1.7	0
0.5	3	2.7	1.7	5
1	3	2.7	1.7	10
2	3	4.0	2.5	12
3	3	5.4	3.4	14
4	3	6.7	4.2	16
5	3	8.0	5.0	18

11. ASSESSMENT OF SAFETY

11.1 Medical, Medication, and Non-Drug Therapy History

At screening, the subject's medical history will be described for the following body systems including significant 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.

Angina onset date must be recorded in each subject's medical history at Screening.

All medications actively being taken (i.e., not including “as needed” or PRN medications that are not actually taken during study participation) 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 subject or be indicative of an underlying condition that would put the subject at risk.

Heparin should not be used during or within 24 hours prior to administration of the investigational product as it has been found to interfere with homing and migration of CD34+ cells.[64]

11.2 Physical Examinations

At screening and subsequent study visits, a physical examination will be performed. A complete physical exam assessment includes the following categories: head, eye, ear, nose, throat; respiratory; cardiovascular; gastrointestinal; genitourinary; musculoskeletal; neurological; endocrine/metabolic; blood/lymphatic; dermatologic; psychiatric; allergy.

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.

11.3 Clinical Laboratory Parameters

11.3.1 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), and platelet counts. A hematology assessment will be performed locally on G-CSF Day 5. Hematology can be evaluated in either the fed or fasted state.

11.3.2 **Coagulation**

Coagulation parameters will include prothrombin time (PT; sec) activated partial thromboplastin time (APTT; sec), and international normalized ratio (INR).

11.3.3 **Clinical Chemistry**

The clinical chemistry panel will consist of creatinine, estimated glomerular filtration rate (e-GFR), creatine kinase (CK), electrolytes (sodium, potassium, chloride, and calcium), 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. Clinical chemistry may be evaluated in the fasted or non-fasted state.

11.3.4 **Lipid Panel**

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

11.3.5 **Troponin**

Troponin assessments should be made by local laboratory using the institution's preferred assay method for a cardiac-specific troponin. The same assay method should be used at each time point. Clinically significant increases in troponin from pre-infusion values must be reported as an adverse event.

11.3.6 **Urinalysis**

The urinalysis panel will be assessed by a urine test strip at the site and will evaluate leukocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

11.3.7 **Pregnancy Testing**

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

11.3.8 **Serology**

The following tests will be performed at screening: HIV, hepatitis B and hepatitis C. If the screening serology sample is drawn more than 29 days prior to apheresis, a repeat serology sample must be drawn so that the date of collection is within 29 days of the apheresis date.

11.4 **Vital Signs**

Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), systolic and diastolic blood pressure (mm Hg), height (cm, only at the screening visit) and weight (kg) as indicated for each visit. Blood pressures should be measured after 5 minutes of rest. A full set of vital signs will be measured at screening and during the G-CSF administration visits. On Day 0 (Treatment), before administration of IP, a full set of vitals (including weight) will be collected. At the start of IP administration and at post IP administration timepoints, only blood pressure and pulse rate will be collected. At Day 1, only blood pressure and pulse rate will be collected. At Days 90 and 180 (or at study completion/termination), a full set of vitals will be collected. Additionally, blood pressure and pulse rate will be monitored at the following timepoints (these will not be made part of the clinical database):

- Before, during and after apheresis
- Regularly 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 11.1). 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.

11.5 **Assessment of Major Adverse Cardiac Events**

An independent clinical event classification committee will adjudicate whether AEs during the conduct of the study are deemed MACE. In this study, MACE will be defined as all death, cardiovascular hospitalization, non-fatal myocardial infarction, and stroke.

11.6 **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, regardless of a causal relationship with study participation or treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease that occurs during the study, having been absent at baseline, or – if present at baseline – appears to worsen. An AE includes any event, regardless of the presumed causality between the event and the study or IP.

Note that although angina is a study entry criterion and a study endpoint, a worsening of angina (beyond what a subject considers to be typical/familiar) should be considered an adverse event. It is well-recognized that angina is a common symptom of CMD, and that angina can commonly occur during a cardiac catheterization. Any chest pain that exceeds a 3-point increase on a 10-point pain scale during and up to 30 minutes following a coronary intervention should be captured and reported as an adverse event. This applies to IP infusion and coronary microvascular assessments (invasive CFR assessed by Doppler wire or thermodilution, invasive assessment of IMR, invasive assessment of CBF, and non-invasive assessment of MPR or MFR by PET or MRI).

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.

11.6.1 **Serious Adverse Event**

An 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's designated Pharmacovigilance group (see Section 11.6.6) within 24 hours of becoming aware of the event.

11.6.2 **Non-Serious Adverse Event**

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

11.6.3 **Adverse Events of Special Interest**

The following 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
- Any increase in chest pain more than 3-points on a 10-point pain scale during and up to 30 minutes after the infusion procedure
- Heart rate less than 50 bpm during and up to 30 minutes after the infusion procedure
- Systolic blood pressure less than 80 mmHg during and up to 30 minutes after the infusion procedure
- Occurrence of any clinically significant conduction changes on ECG per the investigator during the infusion procedure or during post-procedure monitoring

11.6.4 **Severity**

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate CTCAE description. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

11.6.5 **Causality**

Causality is a determination of whether there is a reasonable possibility that the IP or a study procedure is etiologically related to/associated with the AE. Causality to G-CSF, the apheresis procedure, the IP, and the IP administration 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 or a study procedure (i.e., does not follow a reasonable temporal relationship to the administration of IP or has a much more likely alternative etiology).
  - No rationale exists for relatedness
- Unlikely related (either 1 or both circumstances are met)
  - Has little or no temporal relationship to the IP or a study procedure
  - A more likely alternative etiology exists
  - Some (perhaps weak) rationale exits for a relatedness
- Possibly related (both circumstances must be met)
  - Follows a reasonable temporal relationship to the administration of IP or a study procedure

‡ From CTC-AE version 5.0

  - An alternative etiology is equally or less likely compared to the potential relationship to the IP or a study procedure
- Probably related (both circumstances must be met)
  - Follows a strong temporal relationship to the administration of IP or a study procedure
  - Another etiology is unlikely or significantly less likely
- Definitely related
  - The evidence provides convincing proof of a relationship to the IP or a study procedure

11.6.6 **Reporting for Adverse Events**

All AEs will be recorded from signing the informed consent until study completion or discontinuation. AEs that occur prior to G-CSF treatment will be considered non-treatment emergent AEs. AEs that occur during or after G-CSF treatment will be considered treatment emergent AEs (TEAEs). 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 11.6.1 and Section 11.6.2, respectively. The investigator will evaluate the severity of each AE and the causal relationship of the event to G-CSF, the apheresis procedure, the IP, and the IP administration procedure (see Section 11.6.4 and Section 11.6.5, respectively). The outcome and action taken also will be recorded on the AE form. Non-serious AEs 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 AND AESIs 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:
[redacted]

The investigator shall comply with applicable local regulations for SAE reporting and also the United States (US) Code of Federal Regulations Title 21 Section 312 [21CFR

312] and any applicable guidance from the US Food and Drug Administration (FDA) for reporting any SAEs.

11.6.7 **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.

11.6.8 **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 11.6.1 and Section 11.6.2
- Severity as defined in Section 11.6.4
- Causal relationship to IP exposure or study-related procedure as defined in Section 11.6.5

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 subject's termination visit, whichever comes first.

12. **DATA MONITORING COMMITTEE**

An independent DMC, consisting of at least 3 independent representatives, including a chairperson, at least one cardiologist, and a biostatistician, will monitor the safety of study participants. The DMC charter includes the details for the DMC responsibilities, qualifications, and key processes. The DMC responsibilities will include (but are not limited to) the following:

- Review and contribute to the development and/or finalization of the DMC charter

- Review the protocol, plans for data safety and monitoring, and any other relevant study documents
- During trial conduct, review reports that present interim safety data and make recommendations pertinent to the safety of trial participants
- Monitor study conduct by reviewing major protocol deviations
- Review any cases for which unblinding of treatment assignments at the study site or by the treating clinician is thought to be necessary to provide an appropriate intervention
- Following periodic review of safety data, make recommendation to Sponsor on whether to continue, terminate, or proceed with modifications

13. STATISTICS

13.1 Sample Size justification

One hundred and five (105) subjects will be randomized in a 4:3 ratio to receive CLBS16 or placebo. Since it is a key objective to determine the effect size and variability of the clinical outcome measures, there is no formal sample size calculation for this study.

13.2 Analysis populations

In accordance with ICH E9, the following population of analysis will be used for all statistical analyses.

13.2.1 Full analysis set

The full analysis set (FAS) will consist of all randomized subjects who received treatment with IP and have at least one post-baseline assessment. Efficacy analyses will be based on the treatment as randomized.

13.2.2 Per-protocol analysis set

The per-protocol analysis set (PPS) will include all subjects in the FAS and exclude subjects who had major protocol deviations that may impact interpretation of study results. Final determination of the PPS will be made at the blinded data review meeting prior to database lock.

13.2.3 Safety analysis set

The safety set (SAF) includes all subjects who have been consented in the study and have received treatment with G-CSF or have undergone apheresis or functional coronary angiography or have received a dose of IP. The safety analysis set may be further subdivided for subjects who received only a subset of the intended procedures. The analysis will be based on the treatment as treated.

13.3 Planned Statistical Analysis

The full statistical analysis plan will be outlined in the statistical analysis plan, which will be finalized before database lock.

13.3.1 Analysis of Demographic and Other baseline Characteristics

Demographic and other baseline characteristics will be summarized using the FAS. Additional summaries will be provided for the SAF as appropriate. Summary statistics will be generated for continuous variables. The number and percentage of subjects will be presented for categorical variables.

13.3.2 Efficacy Analysis

Efficacy endpoints will be analyzed using the FAS and the PPS.

The statistical testing will be performed between CLBS16 and placebo.

The analysis of the mean change from baseline in angina frequency, ETT, CCS, and SAQ that compares the CLBS16 and placebo groups will use two sample t-test. The difference between treatment groups and confidence intervals will be estimated.

For other efficacy endpoints, variables that are continuous will be analyzed using 2 sample t-test. In the event that the model assumptions underlying the t-test are not warranted, the Wilcoxon Rank Sum test with exact method will be used. Variables that are proportions will be analyzed using chi-square test, and the treatment difference and exact 95% CIs will be reported.

13.3.3 Exploratory Analysis

Exploratory endpoints that are continuous will be analyzed using 2 sample t-test. In the event that the model assumptions underlying the t-test are not warranted, the Wilcoxon Rank Sum test with exact method will be used.

Additional exploratory analysis will be conducted to examine on the potential confounding effects of selected concomitant medications on study endpoints will be conducted.

13.3.4 **Safety Analysis**

AEs and other safety endpoints will be summarized using the SAF.

All AEs will be coded using MedDRA. A TEAE is defined as an AE that starts or worsens on or after G-CSF dosing and no more than 14 days after last dose. The number and percentage of subjects with TEAEs will be summarized by MedDRA System Organ Class, High Level Term, and Preferred Term overall, by severity and by relationship to study drug or procedures.

Change from baseline in clinical laboratory tests and vital signs will be summarized. Post-baseline ECG assessment will be summarized with respect to being normal, abnormal (not clinically significant), or abnormal (clinically significant).

The percent of subjects that have at least one MACE and the rate of MACE will be summarized. Time to first MACE or time to death will be explored using KM method. In addition to being analyzed in SAF as treated, MACE will be analyzed as randomized in FAS.

14. **DATA HANDLING AND RECORD KEEPING**

14.1 **Confidentiality Policy**

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

14.2 **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 source documents and data entry of Case Report Forms 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.

14.3 **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.

14.4 **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.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1 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 for Harmonisation (ICH), Good Clinical Practice (GCP), and applicable local and national 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.

15.2 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.

15.3 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 local and national 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.

15.4 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 local and national regulatory authorities of any investigator termination.

16. ETHICS

16.1 Compliance Statement

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

16.2 Participating Centers

Participating clinical sites must have an appropriate IRB governance since they are actively engaged in research and provide informed consent. In the US, the Health Insurance Portability and Accountability Act (HIPAA) and in all regions, applicable local and national 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.

16.3 **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 local and national laws and regulations. Investigators will enroll subjects according to the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All subjects must provide consent before entering into the study according to applicable local and national 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 local and national regulatory requirements. Subjects will be allowed sufficient time to consider participation in the study. By signing the informed consent form, subjects 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.

16.4 **Subject Privacy**

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

16.5 **Risks and Benefits**

CLBS16 is an autologous, minimally-manipulated cell product that is being used in a homologous setting (i.e. naturally occurring vascular repair cells are collected from the vasculature and returned to the vasculature to perform their pre-programmed function, stimulating angiogenesis).[65-69] In multiple studies with autologous, minimally-manipulated CD34 cells in cardiovascular indications, there have never been any events which appeared to be cell-related.

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.

16.6 **Ethics Committee and Regulatory Authorities**

Before enrollment of subjects into this study, the protocol, informed consent form, any promotional material/advertisements, and any other written information to be provided to the subjects 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.

17. **STUDY ADMINISTRATION**

17.1 **Monitoring**

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. The study will be routinely monitored to ensure compliance with the study protocol and the overall quality of data collected. During the on-site or remote interim monitoring 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 will 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 subject has proper consent documentation from the subject and/or subject's authorized representative for study procedures and for the release of medical records, in accordance with site standard operating procedures, and IRB and local and national regulatory guidelines. The investigator or appointed delegate will receive the study monitor during 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.

17.2 **Medical Monitor**

All AEs will be recorded on the AE 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 AE reports.

17.3 **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.

17.4 **Publication Policy**

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

18. SUPPLEMENTS

18.1 Angina/Nitroglycerin Use Diary

INSTRUCTIONS

- For each of the 14 days in the reporting period, fill in the date and the total number of angina episodes/attacks you had that day (enter "0" if you had no angina episodes on a specific day). Enter numerical values (numbers) only.
- Write down what triggered your angina, if anything. Common triggers are exercise, emotions, etc. If there was no trigger, write "none".
- On a scale of 1 to 4, rate the severity of your pain or discomfort during the worst attack of each day: 1=mild, 2=somewhat strong, 3=severe, and 4=very severe.
- Note how long (in minutes) the longest angina attack of the day lasted.
- Record the total number of sublingual doses of nitroglycerin (spray or a tablet that goes under the tongue) you took each day. Enter "0" if none was taken.

Reporting Day	Date	Total # of Angina Attacks for the Day	Triggers (do not use abbreviations)	Worst Severity (1=mild, 2=somewhat strong, 3=severe, 4=very severe)	Longest duration (minutes)	Record TOTAL # of Fast-Acting Sublingual Nitroglycerin Doses (Spray or Tablet) Taken (Do not include patches or extended release)
1						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
2						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
3						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
4						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
5						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____

Reporting Day	Date	Total # of Angina Attacks for the Day	Triggers (do not use abbreviations)	Worst Severity (1=mild, 2=somewhat strong, 3=severe, 4=very severe)	Longest duration (minutes)	Record TOTAL # of Fast-Acting Sublingual Nitroglycerin Doses (Spray or Tablet) Taken (Do not include patches or extended release)
6						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
7						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
8						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
9						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
10						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
11						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
12						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
13						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____
14						# of tablets (0.3, 0.4, or 0.6 mg): _____ # of sprays (400 mcg): _____

Self-check: Did you record a full day's worth of information for each of the reporting days above? □ Yes □ No*
*If not, please tell us which reporting days represent only partial-day data:
_____

18.2 **Seattle Angina Questionnaire**

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or angina over the past 4 weeks**.

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a block at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain, chest tightness, or angina** when doing your **most strenuous** activities?

I have had **chest pain, chest tightness, or angina...**

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness, or angina**?

I have had **chest pain, chest tightness, or angina...**

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness, or angina**?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain, chest tightness, or angina** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain, chest tightness, or angina**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the past 4 weeks, how much has your **chest pain, chest tightness, or angina** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain, chest tightness, or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I **can't stop** thinking or worrying about it	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

18.3 Short Form 36 Questionnaire

QUALITY OF LIFE QUESTIONNAIRE (SF-36v2™ Health Survey)

This survey asks for your views about your health, how you feel and how well you are able to do your usual activities. Answer every question by checking the appropriate response. There are no right or wrong answers. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. Compared to one year ago, how would you rate your health in general now?

Much better	Somewhat better	About the same	Somewhat worse	Much worse
☐	☐	☐	☐	☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous activities.	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several hundred yards	☐	☐	☐
i. Walking one hundred yards	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

QUALITY OF LIFE QUESTIONNAIRE (SF-36v2™ Health Survey)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐	☐	☐	☐	☐
b. Accomplished less than you would have liked	☐	☐	☐	☐	☐
c. Were limited in the kind of work or other activities	☐	☐	☐	☐	☐
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down the amount of time you spent on work or other activities	☐	☐	☐	☐	☐
b. Accomplished less than you would like	☐	☐	☐	☐	☐
c. Did your work or activities less carefully than usual	☐	☐	☐	☐	☐

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

QUALITY OF LIFE QUESTIONNAIRE (SF-36v2™ Health Survey)

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the Past 4 weeks….	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐	☐	☐	☐	☐
b. Have you been very nervous?	☐	☐	☐	☐	☐
c. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d. Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e. Did you have a lot of energy?	☐	☐	☐	☐	☐
f. Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g. Did you feel worn out?	☐	☐	☐	☐	☐
h. Have you been happy?	☐	☐	☐	☐	☐
i. Did you feel tired?	☐	☐	☐	☐	☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

QUALITY OF LIFE QUESTIONNAIRE (SF-36v2™ Health Survey)

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b. I am as healthy as anybody I know	☐	☐	☐	☐	☐
c. I expect my health to get worse	☐	☐	☐	☐	☐
d. My health is excellent	☐	☐	☐	☐	☐

Thank you for completing this very important questionnaire!

18.4 **Intracoronary Cell Delivery Procedure**

19. REFERENCES

1. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, Duvernoy C, Walsh MN, Bairey Merz CN and Committee ACiW. Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography. *J Am Coll Cardiol*. 2015;66:1918-33.
2. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG and Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886-95.
3. Radico F, Cicchitti V, Zimarino M and De Caterina R. Angina pectoris and myocardial ischemia in the absence of obstructive coronary artery disease: practical considerations for diagnostic tests. *JACC Cardiovasc Interv*. 2014;7:453-63.
4. Jespersen L, Hvelplund A, Abildstrom SZ, Pedersen F, Galatius S, Madsen JK, Jorgensen E, Kelbaek H and Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734-44.
5. Jespersen L, Abildstrom SZ, Hvelplund A, Galatius S, Madsen JK, Pedersen F, Hojberg S and Prescott E. Symptoms of angina pectoris increase the probability of disability pension and premature exit from the workforce even in the absence of obstructive coronary artery disease. *Eur Heart J*. 2013;34:3294-303.
6. Shaw LJ, Merz CN, Pepine CJ, Reis SE, Bittner V, Kip KE, Kelsey SF, Olson M, Johnson BD, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Sopko G and Women's Ischemia Syndrome Evaluation I. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health--National Heart, Lung, and Blood Institute--sponsored Women's Ischemia Syndrome Evaluation. *Circulation*. 2006;114:894-904.
7. Camici PG and Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830-40.
8. Phan A, Shufelt C and Merz CN. Persistent chest pain and no obstructive coronary artery disease. *JAMA*. 2009;301:1468-74.
9. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, Dorbala S, Blankstein R, Rimoldi O, Camici PG and Di Carli MF. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation*. 2014;129:2518-27.
10. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Jr. and Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation*. 2000;101:948-54.
11. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO and Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. *JACC Cardiovasc Interv*. 2015;8:1445-53.
12. Heistad DD, Armstrong ML, Marcus ML, Piegors DJ and Mark AL. Augmented responses to vasoconstrictor stimuli in hypercholesterolemic and atherosclerotic monkeys. *Circ Res*. 1984;54:711-8.

13. Sambuceti G, Marzullo P, Giorgetti A, Neglia D, Marzilli M, Salvadori P, L'Abbate A and Parodi O. Global alteration in perfusion response to increasing oxygen consumption in patients with single-vessel coronary artery disease. *Circulation*. 1994;90:1696-1705.
14. Sellke FW, Friedman M, Dai HB, Shafique T, Schoen FJ, Weintraub RM and Johnson RG. Mechanisms causing coronary microvascular dysfunction following crystalloid cardioplegia and reperfusion. *Cardiovasc Res*. 1993;27:1925-32.
15. Gimelli A, Schneider-Eicke J, Neglia D, Sambuceti G, Giorgetti A, Bigalli G, Parodi G, Pedrinelli R and Parodi O. Homogeneously reduced versus regionally impaired myocardial blood flow in hypertensive patients: two different patterns of myocardial perfusion associated with degree of hypertrophy. *J Am Coll Cardiol*. 1998;31:366-73.
16. Pitkanen OP, Nuutila P, Raitakari OT, Ronnemaa T, Koskinen PJ, Iida H, Lehtimaki TJ, Laine HK, Takala T, Viikari JS and Knuuti J. Coronary flow reserve is reduced in young men with IDDM. *Diabetes*. 1998;47:248-254.
17. Yokoyama I, Momomura S, Ohtake T, Yonekura K, Nishikawa J, Sasaki Y and Omata M. Reduced myocardial flow reserve in non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol*. 1997;30:1472-7.
18. Yokoyama I, Ohtake T, Momomura S, Nishikawa J, Sasaki Y and Omata M. Reduced coronary flow reserve in hypercholesterolemic patients without overt coronary stenosis. *Circulation*. 1996;94:3232-8.
19. Wang L, Jerosch-Herold M, Jacobs DR, Jr., Shahar E and Folsom AR. Coronary risk factors and myocardial perfusion in asymptomatic adults: the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Coll Cardiol*. 2006;47:565-72.
20. Pepine CJ, Anderson RD, Sharaf BL, Reis SE, Smith KM, Handberg EM, Johnson BD, Sopko G and Bairey Merz CN. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. *J Am Coll Cardiol*. 2010;55:2825-32.
21. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichek N, Rogers WJ, Walsh EG, Fuisz AR, Kerensky R, Detre KM, Sopko G and Pepine CJ. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstructive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol*. 1999;33:1469-75.
22. Thomson LE, Wei J, Agarwal M, Haft-Baradaran A, Shufelt C, Mehta PK, Gill EB, Johnson BD, Kenkre T, Handberg EM, Li D, Sharif B, Berman DS, Petersen JW, Pepine CJ and Bairey Merz CN. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation. *Circulation Cardiovascular imaging*. 2015;8.

23. Agarwal M, Shufelt C, Mehta PK, Gill E, Berman DS, Li D, Sharif B, Li N, Bairey Merz CN and Thomson LE. Cardiac risk factors and myocardial perfusion reserve in women with microvascular coronary dysfunction. *Cardiovascular diagnosis and therapy*. 2013;3:146-52.
24. Bairey Merz CN, Henry T, Wei J, Corban M, Sandy J, Kotynski C, Lewis M, Schumacher A, Sietsema WK, Losordo DW and Lerman A. Clinical Trial of Autologous CD34 Cell Therapy for Treatment of Coronary Microvascular Dysfunction in Patients With Angina and Non-Obstructive Coronary Arteries. Paper presented at: American Heart Association; 2019; Philadelphia, PA.
25. Henry TD, Lerman A, Wei J, Corban M, Joung S, Kotynski C, Lewis M, Schumacher A, Shah V, Bartel R, Wang J, Sietsema WK, Losordo DW and Bairey Merz CN. Autologous CD34 Cell Therapy for Treatment of Coronary Microvascular Dysfunction In Patients with Angina and Non-obstructive Coronary Arteries. Paper presented at: Society for Cardiovascular Angiography and Interventions 2020 Scientific Sessions Virtual Conference; 2020.
26. Assmus B, Leistner DM, Schachinger V, Erbs S, Elsasser A, Haberbosch W, Hambrecht R, Sedding D, Yu J, Corti R, Mathey DG, Barth C, Mayer-Wehrstein C, Burck I, Sueselbeck T, Dill T, Hamm CW, Tonn T, Dimmeler S and Zeiher AM. Long-term clinical outcome after intracoronary application of bone marrow-derived mononuclear cells for acute myocardial infarction: migratory capacity of administered cells determines event-free survival. *Eur Heart J*. 2014;35:1275-83.
27. Erbs S, Linke A, Schachinger V, Assmus B, Thiele H, Diederich KW, Hoffmann C, Dimmeler S, Tonn T, Hambrecht R, Zeiher AM and Schuler G. Restoration of microvascular function in the infarct-related artery by intracoronary transplantation of bone marrow progenitor cells in patients with acute myocardial infarction: the Doppler Substudy of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial. *Circulation*. 2007;116:366-74.
28. Schachinger V, Assmus B, Honold J, Lehmann R, Hofmann WK, Martin H, Dimmeler S and Zeiher AM. Normalization of coronary blood flow in the infarct-related artery after intracoronary progenitor cell therapy: intracoronary Doppler substudy of the TOPCARE-AMI trial. *Clin Res Cardiol*. 2006;95:13-22.
29. Losordo DW, Henry TD, Davidson C, Sup Lee J, Costa MA, Bass T, Mendelsohn F, Fortuin FD, Pepine CJ, Traverse JH, Amrani D, Ewenstein BM, Riedel N, Story K, Barker K, Povsic TJ, Harrington RA, Schatz RA and Investigators AC. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. 2011;109:428-36.
30. Vrtovec B, Poglajen G, Lezaic L, Sever M, Domanovic D, Cernelc P, Socan A, Schrepfer S, Torre-Amione G, Haddad F and Wu JC. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. *Circ Res*. 2013;112:165-73.
31. Poglajen G, Sever M, Cukjati M, Cernelc P, Knezevic I, Zemljic G, Haddad F, Wu JC and Vrtovec B. Effects of transendocardial CD34+ cell transplantation in patients with ischemic cardiomyopathy. *Circ Cardiovasc Interv*. 2014;7:552-9.

32. Wei J, Mehta PK, Johnson BD, Samuels B, Kar S, Anderson RD, Azarbal B, Petersen J, Sharaf B, Handberg E, Shufelt C, Kothawade K, Sopko G, Lerman A, Shaw L, Kelsey SF, Pepine CJ and Merz CN. Safety of coronary reactivity testing in women with no obstructive coronary artery disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. *JACC Cardiovasc Interv*. 2012;5:646-53.
33. Ford TJ, Ong P, Sechtem U, Beltrame J, Camici PG, Crea F, Kaski JC, Bairey Merz CN, Pepine CJ, Shimokawa H and Berry C. Assessment of Vascular Dysfunction in Patients Without Obstructive Coronary Artery Disease: Why, How, and When. *JACC Cardiovasc Interv*. 2020;13:1847-1864.
34. Ford TJ and Berry C. How to Diagnose and Manage Angina Without Obstructive Coronary Artery Disease: Lessons from the British Heart Foundation CorMicA Trial. *Interv Cardiol*. 2019;14:76-82.
35. Nammas W, Maaniitty T, Knuuti J and Saraste A. Cardiac perfusion by positron emission tomography. *Clin Physiol Funct Imaging*. 2021.
36. Ziadi MC, Dekemp RA, Williams KA, Guo A, Chow BJ, Renaud JM, Ruddy TD, Sarveswaran N, Tee RE and Beanlands RS. Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia. *J Am Coll Cardiol*. 2011;58:740-8.
37. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, Blankstein R, Dorbala S, Sitek A, Pencina MJ and Di Carli MF. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124:2215-24.
38. Doyle M, Fuisz A, Kortright E, Biederman RW, Walsh EG, Martin ET, Tauxe L, Rogers WJ, Merz CN, Pepine C, Sharaf B and Pohost GM. The impact of myocardial flow reserve on the detection of coronary artery disease by perfusion imaging methods: an NHLBI WISE study. *J Cardiovasc Magn Reson*. 2003;5:475-85.
39. Doyle M, Weinberg N, Pohost GM, Bairey Merz CN, Shaw LJ, Sopko G, Fuisz A, Rogers WJ, Walsh EG, Johnson BD, Sharaf BL, Pepine CJ, Mankad S, Reis SE, Vido DA, Rayarao G, Bittner V, Tauxe L, Olson MB, Kelsey SF and Biederman RW. Prognostic value of global MR myocardial perfusion imaging in women with suspected myocardial ischemia and no obstructive coronary disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. *JACC Cardiovasc Imaging*. 2010;3:1030-6.
40. Freed BH, Narang A, Bhave NM, Czobor P, Mor-Avi V, Zaran ER, Turner KM, Cavanaugh KP, Chandra S, Tanaka SM, Davidson MH, Lang RM and Patel AR. Prognostic value of normal regadenoson stress perfusion cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2013;15:108.
41. Fearon WF and Kobayashi Y. Invasive Assessment of the Coronary Microvasculature: The Index of Microcirculatory Resistance. *Circulation Cardiovascular interventions*. 2017;10:e005361.

42. Lee BK, Lim HS, Fearon WF, Yong AS, Yamada R, Tanaka S, Lee DP, Yeung AC and Tremmel JA. Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease. *Circulation*. 2015;131:1054-60.
43. Povsic TJ, Henry TD, Traverse JH, Fortuin FD, Schaer GL, Kereiakes DJ, Schatz RA, Zeiher AM, White CJ, Stewart DJ, Jolicoeur EM, Bass T, Henderson DA, Dignacco P, Gu Z, Al-Khalidi HR, Junge C, Nada A, Hunt AS, Losordo DW and Investigators R. The RENEW Trial: Efficacy and Safety of Intramyocardial Autologous CD34(+) Cell Administration in Patients With Refractory Angina. *JACC Cardiovasc Interv*. 2016;9:1576-85.
44. Lezaic L, Socan A, Poglajen G, Peitl PK, Sever M, Cukjati M, Cernelc P, Wu JC, Haddad F and Vrtovec B. Intracoronary transplantation of CD34(+) cells is associated with improved myocardial perfusion in patients with nonischemic dilated cardiomyopathy. *J Card Fail*. 2015;21:145-52.
45. Wang S, Cui J, Peng W and Lu M. Intracoronary autologous CD34+ stem cell therapy for intractable angina. *Cardiology*. 2010;117:140-7.
46. Musialek P, Tekieli L, Kostkiewicz M, Majka M, Szot W, Walter Z, Zebzda A, Pieniazek P, Kadzielski A, Banys RP, Olszowska M, Pasowicz M, Zmudka K and Tracz W. Randomized transcoronary delivery of CD34(+) cells with perfusion versus stop-flow method in patients with recent myocardial infarction: Early cardiac retention of (9)(9)(m)Tc-labeled cells activity. *Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology*. 2011;18:104-16.
47. Xu J, Lo S, Juergens CP and Leung DY. Assessing Coronary Microvascular Dysfunction in Ischaemic Heart Disease: Little Things Can Make a Big Difference. *Heart Lung Circ*. 2020;29:118-127.
48. Vancheri F, Longo G, Vancheri S and Henein M. Coronary Microvascular Dysfunction. *J Clin Med*. 2020;9.
49. Tonet E, Pompei G, Faragasso E, Cossu A, Pavasini R, Passarini G, Tebaldi M and Campo G. Coronary Microvascular Dysfunction: PET, CMR and CT Assessment. *J Clin Med*. 2021;10.
50. Williams RP, de Waard GA, De Silva K, Lumley M, Asrress K, Arri S, Ellis H, Mir A, Clapp B, Chiribiri A, Plein S, Teunissen PF, Hollander MR, Marber M, Redwood S, van Royen N and Perera D. Doppler Versus Thermodilution-Derived Coronary Microvascular Resistance to Predict Coronary Microvascular Dysfunction in Patients With Acute Myocardial Infarction or Stable Angina Pectoris. *Am J Cardiol*. 2018;121:1-8.
51. Ong P, Safdar B, Seitz A, Hubert A, Beltrame JF and Prescott E. Diagnosis of coronary microvascular dysfunction in the clinic. *Cardiovasc Res*. 2020;116:841-855.
52. Rahman H, Corcoran D, Aetesam-Ur-Rahman M, Hoole SP, Berry C and Perera D. Diagnosis of patients with angina and non-obstructive coronary disease in the catheter laboratory. *Heart*. 2019;105:1536-1542.

53. Schindler TH and Dilsizian V. Coronary Microvascular Dysfunction: Clinical Considerations and Noninvasive Diagnosis. *JACC Cardiovasc Imaging*. 2020;13:140-155.
54. Lanza GA. Diagnostic Approach to Patients with Stable Angina and No Obstructive Coronary Arteries. *Eur Cardiol*. 2019;14:97-102.
55. Konst RE, Damman P, Pellegrini D, van Royen N, Maas A and Elias-Smale SE. Diagnostic approach in patients with angina and no obstructive coronary artery disease: emphasising the role of the coronary function test. *Neth Heart J*. 2021;29:121-128.
56. Keulards DCJ, El Farissi M, Tonino PAL, Teeuwen K, Vlaar PJ, van Hagen E, Wijnbergen IF, de Vos A, Brueren GRG, Van't Veer M and Pijls NHJ. Thermodilution-Based Invasive Assessment of Absolute Coronary Blood Flow and Microvascular Resistance: Quantification of Microvascular (Dys)Function? *J Interv Cardiol*. 2020;2020:5024971.
57. Feher A and Sinusas AJ. Quantitative Assessment of Coronary Microvascular Function: Dynamic Single-Photon Emission Computed Tomography, Positron Emission Tomography, Ultrasound, Computed Tomography, and Magnetic Resonance Imaging. *Circ Cardiovasc Imaging*. 2017;10.
58. Chen C, Wei J, AlBadri A, Zarrini P and Bairey Merz CN. Coronary Microvascular Dysfunction - Epidemiology, Pathogenesis, Prognosis, Diagnosis, Risk Factors and Therapy. *Circ J*. 2016;81:3-11.
59. Ayub MT and Kalra D. Coronary Microvascular Dysfunction and the Role of Noninvasive Cardiovascular Imaging. *Diagnostics (Basel)*. 2020;10.
60. Campeau L. Grading of angina pectoris (letter). *Circulation*. 1976;54:522-523.
61. Campeau L. The Canadian Cardiovascular Society grading of angina pectoris revisited 30 years later. *Can J Cardiol*. 2002;18:371-9.
62. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonell M and Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333-41.
63. McInnis KJ and Balady GJ. Comparison of submaximal exercise responses using the Bruce vs modified Bruce protocols. *Medicine and science in sports and exercise*. 1994;26:103-107.
64. Seeger FH, Rasper T, Fischer A, Muhly-Reinholz M, Hergenreider E, Leistner DM, Sommer K, Manavski Y, Henschler R, Chavakis E, Assmus B, Zeiher AM and Dimmeler S. Heparin disrupts the CXCR4/SDF-1 axis and impairs the functional capacity of bone marrow-derived mononuclear cells used for cardiovascular repair. *Circ Res*. 2012;111:854-62.
65. Asahara T, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G and Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science*. 1997;275:964-967.
66. Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, Wang J, Homma S, Edwards NM and Itescu S. Neovascularization of ischemic myocardium by

human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat Med*. 2001;7:430-436.

67. Kawamoto A, Iwasaki H, Kusano K, Murayama T, Oyamada A, Silver M, Hulbert C, Gavin M, Hanley A, Ma H, Kearney M, Zak V, Asahara T and Losordo DW. CD34-positive cells exhibit increased potency and safety for therapeutic neovascularization after myocardial infarction compared with total mononuclear cells. *Circulation*. 2006;114:2163-9.
68. Peichev M, Naiyer AJ, Pereira D, Zhu Z, Lane WJ, Williams M, Oz MC, Hicklin DJ, Witte L, Moore MA and Rafii S. Expression of VEGFR-2 and AC133 by circulating human CD34(+) cells identifies a population of functional endothelial precursors. *Blood*. 2000;95:952-8.
69. Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, Yoshikawa H, Tsukamoto Y, Iso H, Fujimori Y, Stern DM, Naritomi H and Matsuyama T. Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. *J Clin Invest*. 2004;114:330-8.

INVESTIGATOR ACKNOWLEDGEMENT

A Double-Blind, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of CLBS16 Delivery in Subjects with Coronary Microvascular Dysfunction and Without Obstructive Coronary Artery Disease

PROTOCOL NUMBER: CLBS16-P02

ClinicalTrials.gov Identifier: NCT04614467

Version Number: 9

Version Date: 3 December 2021

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 local and national regulatory requirements.

Investigator Signature Date

Print Name and Title of Investigator