STATISTICAL ANALYSIS PLAN

CLBS16-P02

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

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STATISTICAL ANALYSIS PLAN APPROVAL FORM

CLBS16

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APPROVAL SIGNATURES:

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin converting enzyme
ACT	Active clotting time
AE	Adverse events
ARB	Angiotensin receptor blocker
BMI	Body mass index
CBF	Coronary blood flow
CCS	Canadian Cardiovascular Society
CFR	Coronary flow reserve
CLBS16	Autologous CD34+ cells
CMD	Coronary microvascular dysfunction
CRT	Coronary reactivity testing
ECG	Electrocardiography
ETT	Exercise Tolerance Test
FCA	Functional Coronary Angiography
G-CSF	Granulocyte-Colony Stimulating Factor
HMR	Hyperemic microvascular resistance
HRQoL	Health-related quality of life
IMR	Index of Microcirculatory Resistance
IP	Investigational Product
MACE	Major adverse cardiac events
MedDRA	Medical Dictionary of Regulatory Activities
MET	Metabolic Equivalent of Task
MFR	Myocardial perfusion reserve
MFR	Myocardial flow reserve
MRI	Magnetic Resonance Imaging
NTG	Nitroglycerin
PET	Positron Emission Tomography
SAE	Severe adverse events
SAQ	Seattle Angina Questionnaire
SF-36	Short Form-36
SI	System International
WHODrug	World Health Organization Drug Dictionary

3. INTRODUCTION

This document describes the statistical analyses and data presentations to be performed for this 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.

This analysis plan was developed based on the principles discussed in the International Council on Harmonisation E3 and E9 Guidelines and in reference to protocol CLBS16-P02.

4. OBJECTIVES

4.1. EFFICACY OBJECTIVES

To evaluate the effect size and variability of CLBS16 in subjects with CMD and without obstructive coronary artery disease on coronary microvascular function.

4.2. SAFETY OBJECTIVES

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

4.3. 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:

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 in the protocol. 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 must be on stable cardiovascular medical therapy for at least 30 days prior to screening and must maintain that stable regimen throughout 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). Each subject will be qualified during screening according to a defined functional coronary angiography (FCA) microvascular assessment protocol using a femoral approach. Coronary microvascular function will be assessed based on coronary flow reserve (CFR) and hyperemic microvascular resistance (HMR) in response to intracoronary adenosine and coronary blood flow (CBF) in response to acetylcholine. 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 daily during the G-CSF administration visits. If the white blood cell count exceeds 75,000 cells/µL on any of the 5 days, that day's G-CSF administration 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

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.

ETT, angina and nitroglycerin diary, and HRQoL will also be measured through the 6-month timepoint.

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.

5. ANALYSIS ENDPOINTS

5.1. EFFICACY ENDPOINT

- 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

5.2. SAFETY ENDPOINTS

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

5.3. EXPLORATORY ENDPOINT(S)

- 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 (subjects who have data for CFR)
- 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

6. DETERMINATION OF SAMPLE SIZE

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.

7. METHOD OF ANALYSIS AND PRESENTATION

7.1. GENERAL PRINCIPLES

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

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

7.1.1. MISSING DATA

Angina frequency will be calculated using all days with diary entry during data collection period (2 weeks prior to study visit). For example, if a subject completes diary entries on 10 of 14 days, but missed entries on 4 days, 10 days will be used as denominator in the analysis.

Missing data for time to onset of angina or time to ST segment changes during ETT will not be imputed.

7.1.2. DEFINITION OF STUDY DAY AND VISIT WINDOW

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

Date of assessment/event – date of GCSF dosing

The study day on or after the dose of GCSF will be calculated as:

Date of assessment/event – date of GCSF dosing + 1.

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

Table 1 Visit Analysis Windows for Efficacy

Visit	Scheduled Visit Day	CFR, MPR, MFR, IMR, CBF, ETT (visit window; study days)	Angina Diary, Nitroglycerin use (visit window; study days)	CCS angina class, SAQ, SF-36 (visit window; study days)
Baseline	<=1	<=1	<=1	<=1
Month 3	90	-	D*-135	D*-135
Month 6	180	D*-273	136-273	136-273
Month 12	365	274-386	274-386	274-386

D*: CD34+ dosing day
Note: 3 months postdosing have a visit window of ± 4 days. Subsequent visits postdosing have a visit window of ± 14 days; Month 12 visit has a visit window of ± 21 days.
Note: ETT measurements include time to angina, total exercise time, time to ST depression.

Table 2 Visit Analysis Windows for Safety

Visit	Scheduled Visit Day	Hematology (visit window; study days)	Chemistry (visit window; study days)	Vital Sign (visit window; study days)	ECG (visit window; study days)	Coagulation factors (Visit window; study days)
Baseline	1	<=1	<=1	<=1	<=1	<=1
Day 2	2	2	-	2	-	-
Day 3	3	3	-	3	-	-
Day 4	4	4	-	4	-	-
Day 5	5	5	-	5	-	-
Day 7	7	D*	D*	D*[(a)]	D*[(b)]	-

Visit	Scheduled Visit Day	Hematology (visit window; study days)	Chemistry (visit window; study days)	Vital Sign (visit window; study days)	ECG (visit window; study days)	Coagulation factors (Visit window; study days)
Day 8	8	D*+1	D*+1	D*+1	D*+1	D*+1
Month 1 after D*	37	D*+2 – 112	D*+2 – 112	-	-	-
Month 3 after D*	97	-		D*+2-142	D*+2-142	-
Month 6 After D*	187	113-280	113-280	143-280	143-280	D*+2 - 280
Month 12 after D*	372	281-393	281-393	281-393	281-393	281-393

D*: CD34+ dosing day
Note: 3 months postdosing have a visit window of ± 4 days. Subsequent visits postdosing have a visit window of ± 14 days. The month 12 assessment will by telephone/mail/email only unless the subject has a previously planned in-person care visit with the site.
(a): on CD34+ dosing date, data include 0,2,4,6 hours after dosing.
(b): on CD34+ dosing date, data include 0,2,6 hours after dosing.

7.2. ANALYSIS SET

7.2.1. 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.

7.2.2. 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.

7.2.3. 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 IP administration. 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.

7.3. DISPOSITION OF SUBJECTS

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

Major protocol deviations will be summarized.

A summary of screening failures will also be provided.

7.4. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

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

7.5. MEDICAL HISTORY AND CONCURRENT MEDICAL CONDITIONS

All medical history will be coded using MedDRA v23.0. Medical history and concurrent medical conditions will be presented in a data listing and will be summarized.

7.6. MEDICATION HISTORY AND CONCOMITANT MEDICATIONS

All medication history and concomitant medications will be coded by therapeutic classification, subclassification, and medication using the World Health Organization Drug Dictionary (WHODrug Sep 2020). A concomitant medication is defined as a medication that is ongoing as of Study Day 1, ends on or after Study Day 1, or starts on or after Study Day 1.

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

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

7.7. STUDY DRUG EXPOSURE AND COMPLIANCE

Summaries of extent of exposure will include descriptive statistics for the number of G-CSF doses, volume and cell counts of injections, and the actual dose of CLBS16 injected.

Diary compliance will be calculated as the percentage of days during data collection period:

> Diary compliance= (Number of days with diary entries collected during data collection period)/(Number of days of diary entries expected during data collection period) × 100%.

7.8. EFFICACY ANALYSIS

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

7.8.1. EFFICACY ENDPOINTS

Continuous variables will be analyzed using two sample t-test using change from baseline data. 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.

- Angina frequency (number of episodes per day) will be calculated using daily diary data. The baseline value for angina frequency will be the angina frequency measured during the screening period. The number of weekly angina episodes will be monitored in the 2 weeks prior to the month 3, 6 and 12 follow-up visits. Angina frequency will be calculated as 14*(average number of episodes/day).

- CCS angina classification will be graded by the PI at baseline, Day 90, Day 180 and Day 365. The classification system is show in below

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	Description
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

- ETT will be assessed on a treadmill using the modified Bruce protocol. 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.

- The SAQ is a 19-item self-administered questionnaire measuring health status in patients with ischemic heart disease across 5 domains: physical limitation (PL), angina stability (AS), angina frequency (AF), treatment satisfaction (TS), and quality of life (QoL). All domain scores and a summary score (SS; derived from the PL, AF, and QoL domains) range from 0 to 100, with higher scores indicating less angina, fewer physical limitations due to angina, and better QoL. Scoring instruction for SAQ is in appendix B.

- SF-36 is a 36-item, patient-reported survey of patient health. It will be calculated into 8 scaled scores; each scale is transformed into a 0-100 scale. Higher score indicates a better health status. In addition, Physical Component (PCS) and Mental Component Scores (MCS) based on the transformed Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH) scores would be performed. The scoring of SF-36 data would be performed using OPTUM® PRO CoRE Scoring Software.
- Nitroglycerin use will be calculated as 14*(average dose/day).

Variables that are proportions will be analyzed using chi-square test, and the treatment difference and exact 95% CIs will be reported.

7.8.2. EXPLORATORY EFFICACY ENDPOINTS

- ETT-induced angina will be collected if a subject experiences angina during ETT. Missing data will not be imputed for the proportion of subjects with ETT induced ST-segment change.

- ETT induced ST-segment change will be determined based on central reading from EKG tracing during ETT. Missing data will not be imputed for proportion of subject with ETT induced ST-segment

- Change from baseline in peak CFR. The peak CFR is determined based on CFR to intracoronary adenosine. CFR is calculated for the ratio of APV after each adenosine dose (PAPV) and before each adenosine dose (BAPV). The highest CFR value from any adenosine dose will be considered the peak CFR response to intracoronary adenosine. A CFR greater than 2.5 will be considered normal.

- MPR or MFR will be measured by cardiac Magnetic Resonance Imaging (MRI) or cardiac Positron Emission Tomography (PET), a MPR greater than 2.0 or a MFR greater than 2.0 will be considered normal.
- IMR is measured by thermodilution, an IMR less than 25 would be considered normal.

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 may be conducted to examine potential confounding effects of selected concomitant medications on study endpoints.

7.9. SAFETY ANALYSIS

Safety will be monitored and the frequency and proportion of patients experiencing AEs, SAEs and MACE during the 12-month follow-up period will be reported. AEs and other safety endpoints will be summarized using the SAF.

7.9.1. ADVERSE EVENTS

All AEs will be coded using MedDRA v23.0. A TEAE is defined as an AE that starts or worsens on or after G-CSF 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 Common Terminology Criteria for Adverse Events (CTCAE 5.0) grade and by relationship to study drug or procedures.

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

- G-CSF
- Apheresis
- Administration Procedure
- IP

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

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

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

7.9.2. CLINICAL LABORATORY EVALUATIONS

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

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

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

7.9.3. VITAL SIGNS

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

7.9.4. ECGS

Post-baseline ECG assessment will be summarized with respect to being normal, abnormal (not clinically significant), or abnormal (clinically significant).

7.9.5. MACE

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.

7.10. INTERIM ANALYSIS

No interim analysis is planned.

7.11. CHANGES IN THE STATISTICAL ANALYSIS PLAN FROM PROTOCOL

In the protocol, it stated that change from baseline in CBF at 6 months as exploratory endpoint would be analyzed. In the SAP, this endpoint is removed from exploratory endpoint list.

Appendix A 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.

Appendix B Scoring instruction of the SAQ

SAS code for below is available at. There are 5 summary scores within the SAQ, which are calculated as follows:

A. The Physical Limitation scale

The Physical Limitation score corresponds to questions la through Ii. Responses to questions la through Ii should be coded numerically as follows:

I = Extremely Limited

2 = Quite a bit Limited

3 = Moderately Limited

4 = Slightly Limited

5 = Not at all Limited

6 = Limited for other reasons or did not do the activity

If the responses to questions 1a through Ii are not I, 2, 3, 4 or 5 then the response is set to missing. Note that a response of 6 is treated as a missing value. Missing values are assigned the average score for that level of activity. Activities are grouped into 3 levels of exertional requirements. The lowest level includes dressing, walking, and showering (1a, 1b and 1c); the middle level is climbing, gardening, and walking more than a block (1d, 1e and 1f); the highest level includes running, lifting, and sports (1g, 1h and 1i). If any one item in a group is missing, then assign the average value of the other group items to the missing item. If all items in the lowest or the highest level are missing, then assign each item the mean of the items in the middle level. If all items in the middle level are missing, then assign each item the average of the means of the lowest and highest levels. If more than 4 items are missing in this scale, then no reasonable score for this dimension can be calculated. After accounting for any missing items, the physical limitation score is computed by standardizing the mean response of all nine items as follows:

Physical Limitation= 100*(Mean Response- 1)/4

B. The Angina Stability scale

The Angina Stability score corresponds to question 2. Responses to question 2 should be coded numerically as follows:

1 = Much more often

2 = Slightly more often

3 =About the same

4 = Slightly less often

5 = Much less often

6 = I've had no chest pain over the last 4 weeks

If the response is 6 (no chest pain over last 4 weeks) then set the response to 3 (about the same). If the response is missing, then angina stability cannot be computed and will be missing. Otherwise, the angina stability score is computed by standardizing the result as follows:

Angina Stability = 100*(Response - I)/4

C. The Angina Frequency scale

The Angina Frequency score corresponds to questions 3 and 4. Responses should be coded sequentially 1 to 6 in order of increasing health status, with 1 denoting the response associated with the lowest health status. If at least one question response is present, then the angina frequency is computed by standardizing the mean response as follows:

Angina Frequency= 100*(Mean Response-1)/5

D. The Treatment Satisfaction scale

The Treatment Satisfaction score corresponds to questions 5, 6, 7 and 8. Responses should be coded sequentially (1, 2, 3 ...) in order of increasing health status, with 1 denoting the response associated with the lowest health status. If responses to questions 5, 6, 7 and 8 are not values 1, 2, 3, 4, or 5 then the response is set to missing. Note that a response of 6 for question 5 is treated the same as a response of 5, following the clinical logic that having no pills prescribed is equivalent to it being 'not bothersome at all' to take anti-angina! medications. If at least two responses are present, then the treatment satisfaction score is computed by calculating the mean response and standardizing the result as follows:

Treatment Satisfaction= 100*(Mean Response - 1)/4

E. The Quality-of-Life scale

The Quality-of-Life score corresponds to questions 9, 10 and 11. Responses should be coded sequentially 1 to 5 in order of increasing health status, with 1 denoting the response associated with the lowest health status. If the responses to questions 9, 10 and 11 are not values 1, 2, 3, 4 or 5 then the response is set to missing. If at least two responses are present, then the Quality-of-Life score may be computed by standardizing the mean response as follows:

Quality of Life= 100*(Mean Response-1)/4

Appendix C METs

(1) If time≤11 minutes, 0.4×(mins+secs/60)+1.1

(2) If time>11 minutes, (mins+secs/60)-5

Minutes	Stage	MPH	Grade%	METS(ESTIMATED)
0-1	0	1.7	0	1.4
1-2				1.9
2-3				2.3
3-4	0.5	1.7	5	2.7
4-5				3.1
5-6				3.5
6-7	1	1.7	10	3.9
7-8				4.3
8-9				4.7
9-10	2	2.5	12	4.9
10-11				6.0
11-12				7.0
12-13	3	3.4	14	8.2
13-14				9.2
14-15				10.1
15-16	4	4.2	16	11
16-17				11.9
17-18				12.9
18-19	5	5.0	18	13.6
19-20				14.3
20-21				15.0

ACSM's Metabolic Calculations Handbook 1st Edition; Oct., 2006
ACSM's Guidelines for Exercise Testing & Prescription 10th Edition; Feb., 2017

Appendix D Criteria for Identification of Clinically Significant Laboratory Values

Hematology - Criteria for Clinically significant values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/□L	>600 x 10^3/□L
	SI	<75 x 10^9/L	>600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Chemistry - Criteria for Clinically significant values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 □mol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI		>177 □mol/L
Blood urea nitrogen	Conventional		>30 mg/dL
	SI		>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
CPK	Both	--	>5x ULN
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, GGT=□-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix E Criteria for Clinically Significant Values and Changes from Baseline of Vital Signs Criteria

Parameter	Unit	Lower Criteria	Upper Criteria	Change Relative to Baseline
Pulse	bpm	<50	>120	Increase of ≥ 15 beats/min
				Decrease of ≥ 15 beats/min
Systolic blood pressure	mm Hg	<85	>180	Increase of ≥ 20 mm Hg
				Decrease of ≥ 20 mm Hg
Diastolic blood pressure	mm Hg	<50	>110	Increase of ≥ 15 mm Hg
				Decrease of ≥ 15 mm Hg
Body temperature	°C	< 35.6	>37.7	

Both the criterion value and the change from Baseline must be met.

8. REFERENCES

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