Clinical Trial Protocol: 1002-01

Study Title:	Randomized, Double-Blind, Placebo-Controlled Phase I/II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with a Myocardial Infarction and Ischemic Left Ventricular Dysfunction (**ALL**ogeneic Heart **ST**em Cells to **A**chieve Myocardial **R**egeneration, **ALLSTAR**)
Study Number:	1002-01
Study Phase:	Phase I/II
Product Name:	CAP-1002 Allogeneic Cardiosphere-Derived Cells
IND Number:	15118
Indication:	Treatment and/or prevention of left ventricular dysfunction following myocardial infarction
Lead Investigators:	[redacted]
Sponsor:	Capricor, Inc.
Medical Monitor:	[redacted]

ALLSTAR
ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration

Original Protocol:	15 May 2012
Amendment 1:	14 June 2012
Amendment 2:	26 June 2012
Amendment 3:	30 January 2013
Amendment 4:	13 June 2013
Amendment 5:	25 October 2013
Amendment 6:	01 December 2014
Amendment 7:	15 May 2015
Amendment 7.1:	05 June 2015
Amendment 8:	15 January 2016
Amendment 8.1:	22 February 2017

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SYNOPSIS

Sponsor: Capricor, Inc.

Name of Finished Product:
CAP-1002 Allogeneic Cardiosphere-Derived Cells

Name of Active Ingredient:
Allogeneic Cardiosphere-derived stem cells

Study Title:
Randomized, Double-Blind, Placebo-Controlled Phase I/II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with a Myocardial Infarction and Ischemic Left Ventricular Dysfunction (**ALL**ogeneic Heart **ST**em Cells to **A**chieve Myocardial **R**egeneration, **ALLSTAR**)

Study Number: 1002-01

Study Phase: Phase I/II

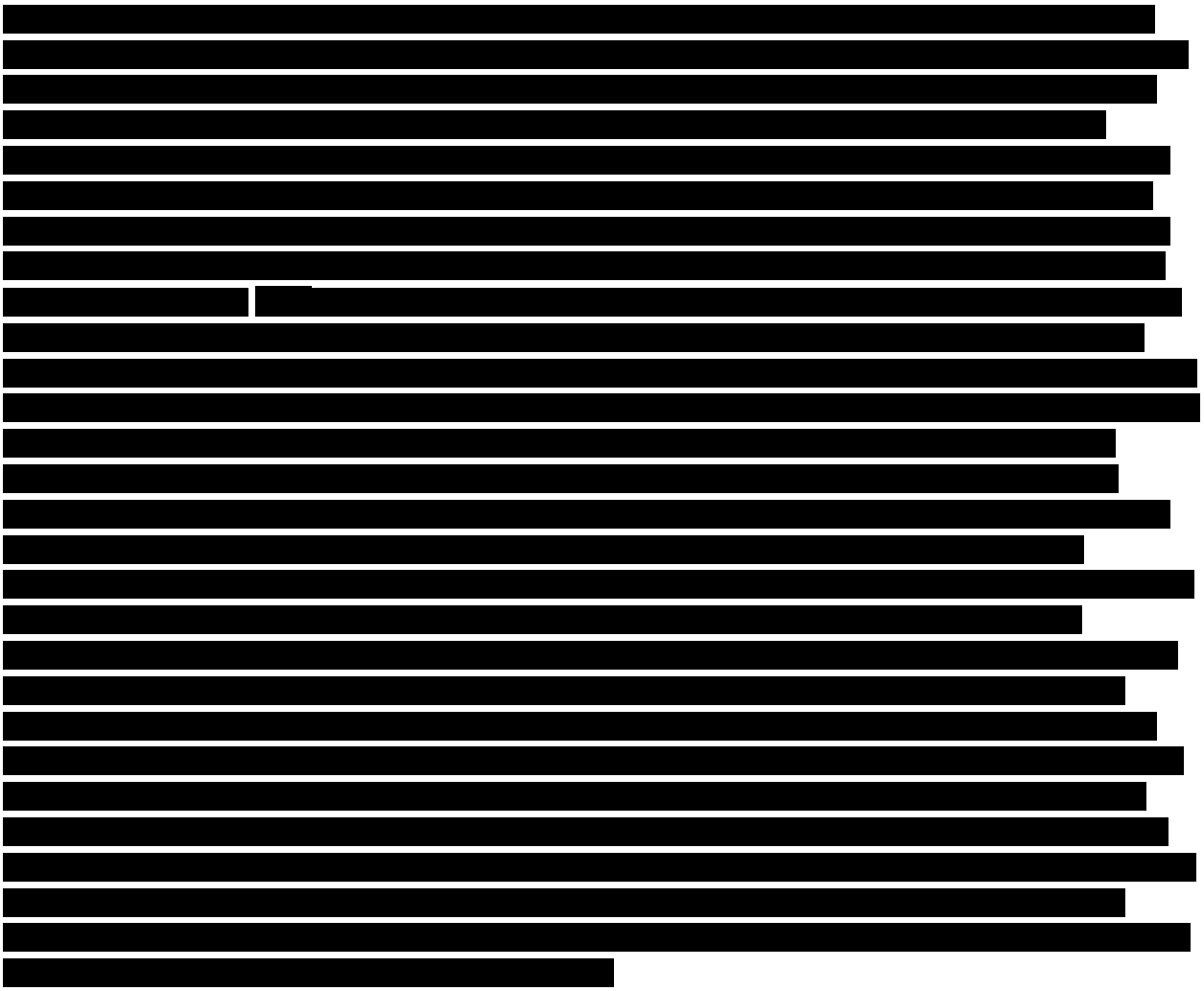
Primary Safety Objective:
The primary safety objective is to determine the safety profile of CAP-1002 administered by intracoronary infusion in subjects with ischemic left ventricular dysfunction and a previous myocardial infarction (MI); specifically, to test the null hypothesis that the incidence rate of the primary safety endpoint (composite of peri-procedural clinical events) differs by no more than 0.20 between treatment groups.

Primary Efficacy Objective:
The primary efficacy objective is to evaluate whether administration of CAP-1002 by intracoronary infusion may result in structural cardiac benefits for subjects with ischemic left ventricular dysfunction and a previous MI as measured by infarct size expressed as a percent of left ventricular mass 12 months after infusion; specifically, to test the hypothesis that CAP-1002 is superior to placebo in reducing infarct size, expressed as a percent of left ventricular mass, 12 months after infusion, either in all subjects combined or in subjects with recent MI (≤ 90 days before infusion).

Secondary Objectives:
The secondary safety objective is to compare the safety profiles of CAP-1002 and placebo over 12 months based on pre-specified clinical events and development of increased HLA antibody levels.

The secondary efficacy objective is to evaluate whether administration of CAP-1002 by intracoronary infusion may result in other left ventricular structural or functional cardiac benefits for subjects with ischemic left ventricular dysfunction and a previous MI. Also evaluations will investigate whether administration of CAP-1002 may result in clinical or biomarker benefits for subjects with ischemic left ventricular dysfunction and a previous MI.

Study Design:



In Phase 2, the Primary Randomized Cohort will enroll up to approximately 103 subjects with a previous myocardial infarction (MI) and resultant ischemic left ventricular dysfunction meeting all inclusion and no exclusion criteria. The Primary Randomized Cohort will include the Recent and Chronic MI strata (n= approximately 51-52 per stratum). These 103 subjects will be randomized in a double-blind fashion to receive either CAP-1002 or placebo (collectively referred to as Investigational Product [IP]) in a 2:1 ratio favoring CAP-1002 to achieve up to 93 subjects with complete 12 month data (assumes 10% non-completion rate and 103 subjects randomized). After completion of the screening procedures and meeting all inclusion and exclusion criteria, study subjects will be randomized to receive CAP-1002 or placebo administered via intracoronary infusion. All subjects in the Primary Randomized Cohort will be followed at week 2 and at months 1, 3, 6 and 12 after planned CAP-1002 or placebo infusion. Efficacy will be assessed at all specified post-infusion visits, with the 12 month visit being the primary efficacy endpoint. An administrative interim analysis of the final 6 month data will be performed when all subjects in the Primary Randomized Cohort have completed the 6 month visit to assist in planning Phase III studies.

The double-blind, placebo-controlled design of the Primary Randomized Cohort will maximize

the study's ability to assess both safety and efficacy, as both may be subject to bias from the perspective of Investigators and subjects.

The Exploratory Randomized Cohort will enroll up to 17 subjects in addition to the Primary Randomization Cohort. Exploratory Randomized Cohort subjects are those subjects who are mismatched against all available donors. The Exploratory Randomized Cohort will also include Recent and Chronic subjects (up to n=8-9 per stratum). The Exploratory Randomized Cohort will be randomized in a double-blind fashion as described in the Primary Randomized Cohort. The Exploratory Randomized Cohort will undergo the same tests as all other subjects based on the schedule of events. This group will be analyzed separately from the Primary Randomized Cohort using descriptive analyses to assess the prevalence and impact on safety and efficacy, if any.

The Primary Randomized Cohort will consist of up to approximately 103 subjects who can be matched to receive IP from one or more donor. A match is achieved when a subject is found at screening to have no antibodies against a donor's HLA antigens (i.e. no donor specific antibodies [DSAs]). Subjects that are mismatched to all available donors will be enrolled into a Phase II Exploratory Randomized Cohort to gather information on potential differences in safety/efficacy. A mismatch situation occurs when a subject is found at screening to have DSAs against all available donors. Up to 17 subjects will be enrolled into the Phase II Exploratory Randomized Cohort.

These Exploratory Randomized Cohort subjects will be randomized independently from the Primary Randomized Cohort. The Exploratory Randomized Cohort is designed to assess the potential effect of donor mismatching, if any, on the primary safety and efficacy endpoints. Using a distinct arm in the study design allows for the inclusion of all subjects meeting eligibility criteria, but preserves the design integrity of the Phase II Randomized Cohort.

Study Population:

When fully enrolled, the ALLSTAR study will include a total of up to approximately 134 subjects with ischemic left ventricular dysfunction and a previous MI. Of these, up to approximately 83 will be treated (infused) with CAP-1002 (n=14 Safety Cohort, n=69 Primary Randomized Cohort) and up to approximately 34 will receive placebo (Primary Randomized Cohort only). Up to 17 subjects may be enrolled into the Phase II Exploratory Randomized Cohort. However, since this group is exploratory in nature, enrollment of the Primary Randomized Cohort will define the end of the study; that is, once the Primary Randomized Cohort is fully enrolled, the study will be considered closed for further subject enrollment.

Test Product, Dose, and Mode of Administration:

[redacted]

[redacted]

Inclusion Criteria:

1. History of MI (STEMI or NSTEMI) within the prior 12 months due to a coronary artery event and evidenced by at least two of the following: typical ischemic symptoms, serial ST-T changes (new ST elevation or new left bundle block) and/or elevated troponin or CK-MB >5 times the upper limit of normal. Also at least one of the following: development of pathological Q wave ECG changes, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormalities.
    - The following assessments will be permitted within 28 days immediately following the subject's MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, and platelet count). All other screening tests, including the subject's cardiac MRI and CT (chest, abdomen, pelvis), must be conducted greater than 28 days post-MI. *Infusion must occur within 28 days of the first screening procedure that is performed greater than 28 days post-MI.* Relevant safety laboratory sample collections (e.g., chemistry, hematology, urinalysis) may need to be repeated as they must be obtained within 28 days of the subject's infusion.
2. History of percutaneous coronary intervention (PCI), with stent placement resulting in TIMI flow = 3, in the coronary artery supplying the infarcted, dysfunctional territory and through which the treatment will be infused.
3. At least one assessment of left ventricular ejection function (LVEF) ≤0.45 as determined by any one of the standard modalities (echocardiography, ventriculogram, nuclear imaging, CT and/or MRI) prior to or during the screening period.
    - For subjects that fulfill the criteria of Recent MI (i.e., within 90 days of MI) *at time of screening visit*: assessment must be post-reperfusion after index MI and be the most recent test prior to or during the screening period.
    - For subjects that fulfill the criteria of Chronic MI (i.e., greater than 90 days from MI) *at time of screening visit*: assessment must be at least 21 days post-reperfusion after index MI and the most recent test prior to or during the screening period.

      Note: subjects may screen as a Recent MI but be randomized into the Chronic MI strata if the infusion date is > 90 days post-MI.
4. Left ventricular infarct size of ≥ 15% of left ventricular mass in the qualifying infarct-related region to be infused as determined by centrally read screening MRI, with associated thinning and/or hypokinesis, akinesis, or dyskinesis, with no large aneurysmal area in the infarcted regions.
5. No further revascularization clinically indicated at the time the subject is assessed for participation in the clinical trial.
6. Ability to provide informed consent and follow-up with protocol procedures.
7. Age ≥18 years.

Exclusion Criteria:

1. Subjects with a history of coronary artery bypass surgery, and a patent graft (arterial or saphenous vein graft) attached to the coronary artery to be infused.
2. Diagnosed or suspected myocarditis.
3. History of cardiac tumor, or cardiac tumor demonstrated on screening MRI.
4. History of acute coronary syndrome in the 4 weeks prior to study infusion.
5. History of previous stem cell therapy.
6. History of radiation treatment to the central or left side of thorax.
7. Current or history (within the previous 5 years) of systematic auto-immune or connective tissue disease including, but not limited to, giant cell myocarditis, cardiac or systemic sarcoidosis, Dressler's syndrome, chronic, recurrent or persistent pericarditis.
8. History of or current treatment with immunosuppressive, anti-inflammatory, or other agents to treat manifestations of systemic immunologic reactions, including chronic systemic corticosteroids, biologic agents targeting the immune system, anti-tumor and anti-neoplastic drugs, anti-VEGF, or chemotherapeutic agents within 3 months prior to enrollment.
9. Prior ICD and/or pacemaker placement where study imaging site has not been trained and certified specifically for this protocol to conduct cardiac MRI in subjects with ICD and/or pacemaker placement.
    a. Presence of a pacemaker and/or ICD generator with any of the following limitations/conditions are excluded:
        i. Manufactured before the year 2000,
        ii. Leads implanted < 6 weeks prior to signing informed consent,
        iii. Non-transvenous epicardial, abandoned, or no-fixation leads,
        iv. Subcutaneous ICDs,
        v. Leadless pacemakers,
        vi. Any other condition that, in the judgement of device-trained staff, would deem an MRI contraindicated.
    b. Pacemaker dependence with an ICD (Note: pacemaker-dependent candidates without an ICD are not excluded).
    c. A cardiac resynchronization therapy (CRT) device implanted < 3 months prior to signing informed consent.
10. Estimated glomerular filtration rate < 30 mL/min.
11. Participation in an ongoing protocol studying an experimental drug or device, or participation in an interventional clinical trial within the last 30 days.
12. Diagnosis of arrhythmogenic right ventricular cardiomyopathy.
13. Current alcohol or drug abuse.
14. Pregnant/nursing women and women of child-bearing potential that do not agree to use at least two forms of active and highly reliable method(s) of contraception. Acceptable methods of contraception include contraceptive pills, depo-progesterone injections, a barrier contraceptive such as a condom with or without spermicide cream or gel, diaphragms or cervical cap with or without spermicide or gel, or an intrauterine device (IUD).
15. Human Immunodeficiency Virus (HIV) infection.
16. Viral hepatitis.
17. Uncontrolled diabetes (HbA1c >9%).
18. Abnormal liver function (SGPT/ALT > 3 times the upper reference range) and/or abnormal hematology (hematocrit < 25%, WBC < 3000 µl, platelets < 100,000 µl) studies without a reversible, identifiable cause.

19. Sustained ventricular tachycardia (VT) or non-sustained ventricular tachycardia > 30 beats, not associated with the acute phase of a previous MI (> 48 hours after the MI onset) or a new acute ischemic episode.
20. Ventricular fibrillation not associated with a new acute ischemic episode.
21. New York Heart Association (NYHA) Class IV congestive heart failure.
22. Evidence of tumor on screening chest/abdominal/pelvic (body) CT scan.
23. Any prior transplant.
24. Known hypersensitivity to dimethyl sulfoxide (DMSO).
25. Known hypersensitivity to bovine products.
26. Any malignancy within 5 years (except for in-situ non-melanoma skin cancer and in-situ cervical cancer) of signing the ICF.
27. Any condition or other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for the study.

Duration of Treatment:

Treated subjects (those who have received intracoronary infusion of CAP–1002 or placebo) will be followed for a total of 12 months. Subjects who agree to participate in the annual follow-up will then be contacted annually through five years post-treatment (post-infusion).

Safety Assessments:

The primary safety endpoint is the one-month post intracoronary infusion proportion of subjects experiencing any of the following adjudicated events:

1. Acute myocarditis possibly attributable to CAP-1002 or placebo, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002 or placebo, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered with placebo.
2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting, or during routine ECG monitoring while hospitalized.
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
4. Major adverse cardiac event (MACE), defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or CK-MB levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be accompanied by symptoms of ischemia > 20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

Separate strata will be evaluated for subjects with a Recent MI and with a Chronic MI. The

following adjudicated events will be evaluated as secondary safety endpoints during the twelve-month follow- up period:

1. Acute myocarditis possibly attributable to CAP-1002 or placebo, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002 or placebo, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo.
2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with prior ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting or during routine ECG monitoring while hospitalized.
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
4. Major adverse cardiac event (MACE), defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or CK-MB levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be accompanied by symptoms of ischemia > 20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
5. New cardiac tumor formation on MRI imaging.
6. Any hospitalization due to a cardiovascular cause or related to CAP-1002 or placebo infusion.
7. Any inter-current cardiovascular illness or one related to CAP-1002 or placebo infusion, which prolongs hospitalization. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin and CK-MB will be obtained approximately every 8 hours for the first 24 hours after infusion.
8. New TIMI flow ≤1, following intracoronary infusion of CAP-1002 or placebo.
9. Development of, or an increase in the frequency of, ventricular tachycardia with a duration of 30 beats or longer ascertained by periodic, protocol-mandated 24 hour ambulatory ECG monitoring.
10. Development of increased anti-HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor.

Efficacy Assessments:

The primary efficacy endpoint is the percent change from baseline in MRI assessment of infarct size as a percent of left ventricular mass 12 months after administration of treatment (either CAP-1002 or placebo).

The following will be evaluated as secondary efficacy endpoints during the six-month and twelve-month follow-up periods:

Global LV Function measures

1. Percent change and change from baseline in MRI assessment of LVEF
2. Percent change and change from baseline in MRI assessment of left ventricular end-diastolic and end-systolic volumes indexed to BSA

Structural measures

3. Change from baseline in MRI assessment of infarct size as a percent of left ventricular mass
4. Percent change and change from baseline in MRI assessment of infarct size expressed in grams
5. Percent change and change from baseline in MRI assessment of viable mass expressed in grams

Regional measure

6. Percent change and change from baseline in MRI assessment of function in the region which received CAP-1002 therapy

Clinical function/status measures

7. Percent change and change from baseline in distance covered in six minute walk test
8. Change from baseline in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores (Total score, Physical Dimension score, and Emotional Dimension score)
9. Change from baseline in Patient Global Assessment (PGA) score

Biomarker

10. Percent change and change from baseline in NT-proBNP
11. Change from baseline in log transformed NT-proBNP

Additional detail regarding secondary endpoint analyses can be found in the Statistical Analysis Plan (SAP).

Statistical Methods:
The safety analysis population will consist of all subjects who received an infusion of either CAP-1002 or placebo. The primary efficacy analysis population in the Randomized Cohort (Primary Modified Intent-to-Treat (mITT) Population, Exploratory mITT Population) will consist of all subjects in the Safety Population who had a baseline observation and at least one post-baseline observation. Demographics and baseline characteristics will be summarized and reported. The Safety Cohort subjects will be summarized and analyzed distinctly from the Randomized Cohorts due to the unblinded nature of the treatment intervention. Similarly, the Exploratory Randomized Cohort of mismatched subjects will also be summarized distinctly from the Primary Randomized Cohort. Details on additional analysis populations will be addressed in the SAP.

Alpha for the study will be controlled by using a closed testing procedure. The primary efficacy analyses will be performed for the analysis population using a modified intent-to-treat population with post-baseline outcome data using a longitudinal mixed effects model. The final analysis will test the hypothesis after 12 months of treatment.

Primary Safety Endpoint: Point estimates and confidence intervals of the proportion of subjects that experience acute myocarditis possibly attributable to CAP-1002 (diagnosed with consideration of clinical context and accompanied by humoral or cellular immune reaction

specific to CAP-1002), death due to ventricular tachycardia or ventricular fibrillation, sudden unexpected death, or a major adverse cardiac event (MACE), defined as the composite incidence of death, non-fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant within the first month post-infusion will be calculated.

Secondary Safety Endpoints: Descriptive analyses of all secondary safety endpoints will be performed using percentages, means, and ranges where appropriate. For incidence rates, two-sided 95% confidence intervals will be constructed for the differences between CAP-1002 and placebo and a two-sided Fisher Exact test will be used for between-treatment comparisons; the Wilcoxon-Mann-Whitney test will be used to compare distributions and ordinal outcomes between randomized treatments. There will be no adjustments for multiple safety assessments by the DSMB and at the interim analyses; a two-sided p=0.05 will be used to establish statistical significance.

Primary Efficacy Endpoint: The primary efficacy endpoint is the percent change from baseline in MRI assessment of infarct size as a percent of left ventricular mass 12 months after administration of treatment (either CAP-1002 or placebo). The primary efficacy hypothesis is that CAP-1002 is superior to placebo in reducing infarct size in either all subjects combined ("full group") or in subjects with recent MI ("subgroup"). A closed testing procedure will be used so that strong control of type 1 error is maintained.

The primary analysis will be a longitudinal mixed effects model. The response variable of percent change from baseline in infarct size as a percent of left ventricular mass will be modeled with the fixed categorical effects of treatment group and time (6 and 12 months), as well as a continuous fixed covariate of baseline infarct size. Intercept and subjects will be treated as random in this mixed effects model. The primary hypothesis will be tested using the estimated treatment effect compared to placebo at 12 months. An additional test will compare the treatments at 6 months and will be considered secondary. Model results will be provided for fixed affects and estimates for each level of each affect.

Secondary Efficacy Endpoints: Data analyses will be performed in a manner consistent with the primary efficacy endpoints. Secondary efficacy analyses will employ the same longitudinal modeling strategy as for the primary efficacy endpoint but will be based on an alpha of 0.05 without controlling for multiplicity. All comparisons in the secondary analyses will be based on a null hypothesis of no difference in the endpoint between subject administered CAP-1002 as compared to placebo.

Exploratory Randomized Cohort Analysis: Presence of DSAs (mismatched) against all available donors: The exploratory analysis is designed to evaluate the prevalence of mismatched subjects, as well as the safety and efficacy profiles within the enrolled population. A review and descriptive comparison of safety and efficacy between the Primary Randomized Cohort and the Exploratory Randomized Cohort will be performed, which preserves the design integrity of the Primary Randomized Cohort. The Exploratory Randomized Cohort sample size was estimated

based on DSA results observed in the Safety Cohort, where approximately 14% of the screened subjects would have been mismatched to all available donors, i.e., assuming at 14% rate of mismatch, approximately 120 subjects would be screened to achieve enrollment of 103 in the matched Primary Randomized Cohort, thus yielding up to 17 subjects enrolled in the mismatched Exploratory Randomized Cohort.

Date of Original Approved Protocol: 14 Jun 2012

Date of Most Recent Protocol Amendment (if applicable): 15 Jan2015

List of Abbreviations and Definitions of Terms

µl	Microliter
ADC	Adipose-Derived Cell
AE	Adverse Event
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase (same as SGPT)
AMI	Acute Myocardial Infarction
AST	Aspartate aminotransferase (same as SGOT)
Atm	Atmospheres
β-HCG	Beta Human Chorionic Gonadotropin
BMMNC	Bone Marrow Mononuclear Cell
BUN	Blood urea nitrogen
C	Celsius
CCU	Critical (or Coronary) Care Unit
CDC	Cardiosphere Derived Cell
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CK-MB	Creatine phosphokinase MB isoenzyme
CMV	Cytomegalovirus
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Cardiac Resynchronization Therapy
CS	Clinically Significant
CSC	Cardiac Stem Cell
CT	Computerized Tomography
DMSO	Dimethyl Sulfoxide
DSA	Donor-Specific Antibody
DSMB	Data Safety Monitoring Board

EBV	Epstein-Barr Virus
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISpot	Enzyme-Linked Immunosorbent Spot
ESR	Expedited Safety Report
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B Surface Antigen
Hct	Hematocrit
HCV	Hepatitis C Virus
HF	Heart Failure
Hgb	Hemoglobin
HbA1c	Glycosylated Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IAP	Interim Analysis Plan
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
K	Potassium

Kg	Kilogram
LDH	Lactate dehydrogenase
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
M	Million
MACE	Major Adverse Cardiac Event
Mcg	Microgram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
Min	Minute
mL	Milliliter
MLHFQ	Minnesota Living with Heart Failure Questionnaire
Mm	Millimeters
mmol	Millimole
MRI	Magnetic Resonance Imaging
MSC	Mesenchymal Stem Cell
Na	Sodium
NHLBI	National Heart, Lung and Blood Institute
NT-proBNP	N-terminal pro-hormone brain natriuretic peptide
NYHA	New York Heart Association
OTW	Over The Wire
P	Probability
PCI	Percutaneous Coronary Intervention
PGA	Patient Global Assessment
PRA	Panel Reactive Antibodies

PSP	Patient Specific Probability
PTT	Activated Partial Thromboplastin Time
RBC	Red blood cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short Form (health survey) - 36 questions
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPRO	Serious Procedure Related Outcome
TIMI	Thrombolysis In Myocardial Infarction
UA	Urinalysis
VF	Ventricular Fibrillation
VGEF	Vascular Endothelial Growth Factor
VT	Ventricular Tachycardia
WBC	White Blood Cell
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1 INTRODUCTION

The principal goal of the proposed Phase I/II study is to examine the safety of intracoronary administration of allogeneic cardiosphere-derived cells (CAP-1002) 4 weeks to 12 months following MI. [redacted]

1.1 Summary of Preclinical Data

[redacted]

[redacted]

1.2 Summary of Clinical Data

1.2.1 Other Cell Therapies

There have been numerous clinical studies to date in which cell therapies have been infused down a coronary artery. The major conclusion of those studies is that the procedure is safe. Efficacy has been a more confounding issue. Bone marrow mononuclear cells (BMMNCs), by far the cell type most extensively studied clinically, have been used repeatedly in acute MI (AMI) patient populations and have shown functional benefits that were marginally positive (Huikuri et al., 2008; Schachinger et al., 2004; Tendera et al., 2009) mixed (Janssens et al., 2006; Roncalli et al., 2011), transient (Meyer et al., 2006; Wollert et al., 2004), or completely negative (Hirsch et al., 2011; Lunde et al., 2006; Wohrle et al., 2010). A meta-analysis of 10 clinical trials involving 698 patients evaluated the overall benefit (Lipinski et al., 2007). Patients receiving cell therapy had an improvement of left ventricular ejection fraction (LVEF) by 3.0% compared to placebo-treated patients. Infarct size and end-systolic volume were significantly reduced in cell-treated patients by 5.6% and 7.4mL, respectively. This analysis and others (Martin-Rendon et al., 2008; Zhang et al., 2009) have also indicated that intracoronary BMMNC therapy has a positive safety profile in AMI patients: no increased incidence of arrhythmias or increased arrhythmia inducibility, no excess proclivity to target- vessel restenosis or repeat revascularization, and no evidence of increased tumorigenesis have been reported. Long-term follow-up data are now emerging from these early studies which also point toward unanticipated benefits on clinical endpoints. In the REPAIR-AMI trial (Schachinger et al., 2006) the incidence of the pre-specified cumulative endpoint of death, MI, or necessity for revascularization was significantly lower at one year. Likewise, the combined endpoint of death, recurrence of MI, and re-hospitalization for heart failure (HF) was reduced. These favorable clinical outcomes were sustained at two years (Assmus et al., 2010). Promising results have also been reported with transplantation of BMMNCs in small trials of patients with chronic cardiomyopathy (Bolli, Jneid, & Dawn, 2005; Dohmann et al., 2005; Perin et al., 2003; Perin et al., 2004; Strauer et al., 2005). However, two rigorous, prospective, randomized, double-blinded studies where autologous BMMNCs were administered either 2- 3 weeks post-MI (LateTIME, (Traverse et al., 2011)) or in a HF population (FOCUS-CCTRN, (Perin et al., 2012)), showed no significant benefits on cardiac function or remodeling.

Mesenchymal stem cells (MSCs), or a more selected subset of mesenchymal precursor cells, have been utilized in several clinical studies and can be used from an allogeneic source. Allogeneic MSCs delivered intravenously in AMI patients have shown modest functional improvements (both cardiac and lung as most cells track to the lungs when given intravenously)

in an early phase study (Hare et al., 2009) that has led to a follow-on study. Allogeneic mesenchymal precursor cells have been utilized in patients with HF and shown a significant reduction in MACE (major adverse cardiac events) in treated patients, but inexplicably no dose-effect in the 3 doses tested and no impact on the parameters of cardiac function examined (Perin, 2011). Given the allogeneic nature of the product, PRAs (panel reactive antibodies) and the development of DSAs (donor-specific antibodies) were assessed in this study. Six of 45 patients (13%) developed DSAs against donor HLA class I transiently, with only 2 patients (4%) exhibiting DSAs beyond 1 month, and no patients exhibiting clinical symptoms. Adipose-derived cells (ADCs) can be isolated from autologous sources with some devices under development. ADCs were utilized recently to treat an AMI patient population (APOLLO) and intracoronary infusion led to a respectable reduction in infarct size (Houtgraaf et al., 2012). Intracoronary application of autologous cardiac stem cells (CSCs) in patients after coronary bypass was recently reported as effective in an interim analysis of an early phase study (Bolli et al., 2011).

Collectively, these clinical data 1) show precedence with intracoronary cell infusion and establish a positive safety profile for the delivery method selected for use with CAP-1002; 2) give preliminary evidence that even modest functional benefits can translate into meaningful clinical benefits; 3) point toward a population of post-MI patients who are refractory to therapy with the most commonly used cell type (BMMNCs); 4) create a paradigm for testing an immune response to allogeneic cell products (focused on DSAs 1 month after delivery) and establish expectations as to the immune-related risks involved.

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1.3.1 Information on CAP -1002

[redacted]

[redacted]

[redacted]

[redacted]

1.3.2 Justification for Dose

[redacted]

1.3.3 Risks to Human Subjects

Risks associated with administration of both the study agent and placebo are similar and related primarily to balloon inflation following catheterization. The risks of balloon inflation are largely related to the balloon inflation pressure. As opposed to the usual clinical setting wherein inflation is performed in the setting of a stenosis and inflation pressures are usually 10-16 atmospheres or higher, inflation in this study is performed within a previously placed stent or area of previous occlusion and solely to prevent reflux of the CAP-1002 or placebo infusion with minimal inflation pressure required to stop blood flow. The risk of coronary dissection is estimated to be less than 1-4% in this setting (Assmus et al., 2006; Janssens, et al., 2006; Schachinger, et al., 2006) and were dissection to occur in a previously unstented segment, a stent would be placed if clinically indicated. In CADUCEUS and ALLSTAR Phase I, no complications that necessitated stent placement were reported during CDC infusion or within 24 hours of infusion among the subjects who were randomized to CDCs.

Other risks of the infusion procedure include those risks that are possible with diagnostic coronary angiography. These include risks related to infection, bleeding, hypotension, pain and hematoma at the arterial puncture site (0.4%), arrhythmia (0.38%), sensitivity or allergy to radiographic contrast (0.37%), exposure to radiation, thromboembolism (0.07%), contrast induced nephropathy, myocardial ischemia or infarction (0.05%). Overall, the risk of any complication is approximately 1.4%, and for death is less than 0.1% (Noto et al., 1991).

[redacted]

[redacted]

1.4 [redacted]

[redacted]

[redacted]

[redacted]

2 STUDY OBJECTIVES

2.1 Primary Safety Objective

The primary safety objective is to determine the safety profile of CAP-1002 administered by intracoronary infusion in subjects with ischemic left ventricular dysfunction and a previous myocardial infarction (MI); specifically, to test the null hypothesis that the incidence rate of the primary safety endpoint (a composite of peri-procedural clinical events) differs by no more than 0.20 between treatment groups.

2.2 Primary Efficacy Objective

The primary efficacy objective is to evaluate whether administration of CAP-1002 by intracoronary infusion may result in structural cardiac benefits for subjects with ischemic left ventricular dysfunction and a previous MI as measured by infarct size expressed as a percent of left ventricular mass 12 months after infusion; specifically, to test the hypothesis that CAP-1002 is superior to placebo in reducing infarct size, expressed as a percent of left ventricular mass, 12 months after infusion, either in all subjects combined or in subjects with recent MI ($\leq$ 90 days before infusion).

2.3 Secondary Objectives

The secondary safety objective is to compare the safety profiles of CAP-1002 and placebo over 12 months based on pre-specified clinical events and development of increased HLA antibody levels.

The secondary efficacy objective is to evaluate whether administration of CAP-1002 by intracoronary infusion may result in other left ventricular structural or functional cardiac benefits for subjects with ischemic left ventricular dysfunction and a previous MI. Also evaluations will investigate whether administration of CAP-1002 may result in clinical or biomarker benefits for subjects with ischemic left ventricular dysfunction and a previous MI.

2.4 Safety Assessments

The primary safety endpoint is the one-month post intracoronary infusion proportion of subjects

experiencing any of the following adjudicated events:

1. Acute myocarditis possibly attributable to CAP-1002 or placebo, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002 or placebo, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo.
2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting, or during routine ECG monitoring while hospitalized.
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
4. Major adverse cardiac event (MACE), defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or CK-MB levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be accompanied by symptoms of ischemia > 20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

Separate strata will be evaluated for subjects with a Recent MI and with a Chronic MI. The following adjudicated events will be evaluated as secondary safety endpoints during the twelve-month follow-up period:

1. Acute myocarditis possibly attributable to CAP-1002 or placebo, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002 or placebo, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo.
2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with prior ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting or during routine ECG monitoring while hospitalized.
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
4. Major adverse cardiac event (MACE), defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or CK-MB levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be accompanied by symptoms of ischemia > 20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of

pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.
5. New cardiac tumor formation on MRI imaging.
6. Any hospitalization due to a cardiovascular cause or related to CAP-1002 or placebo infusion.
7. Any inter-current cardiovascular illness or one related to CAP-1002 infusion or placebo, which prolongs hospitalization. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin and CK-MB will be obtained approximately every 8 hours for the first 24 hours after infusion.
8. New TIMI flow ≤1, following intracoronary infusion of CAP-1002 or placebo.
9. Development of, or an increase in the frequency of, ventricular tachycardia with a duration of 30 beats or longer ascertained by periodic, protocol-mandated 24 hour ambulatory ECG monitoring.
10. Development of increased anti-HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor.

2.4.1 Efficacy Assessments

The primary efficacy endpoint is the percent change from baseline in MRI assessment of infarct size as a percent of left ventricular mass 12 months after administration of treatment (either CAP-1002 or placebo). The following will be evaluated as secondary efficacy endpoints during the six-month and twelve-month follow-up periods:

Global LV Function Measures

1. Percent change and change from baseline in MRI assessment of LVEF
2. Percent change and change from baseline in MRI assessment of left ventricular end-diastolic and end-systolic volumes indexed to BSA

Structural measures

3. Change from baseline in MRI assessment of infarct size as a percent of left ventricular mass
4. Percent change and change from baseline in MRI assessment of infarct size expressed in grams
5. Percent change and change from baseline in MRI assessment of viable mass expressed in grams

Regional measure

6. Percent change and change from baseline in MRI assessment of function in the region which received CAP-1002 therapy

Clinical function/status measures

7. Percent change and change from baseline in distance covered in six minute walk test
8. Change from baseline in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores (Total score, Physical Dimension score, and Emotional Dimension score)
9. Change from baseline in Patient Global Assessment (PGA) score

Biomarker

10. Percent change and change from baseline in NT-proBNP
11. Change from baseline in log transformed NT-proBNP

Additional detail regarding secondary endpoint analyses can be found in the SAP.

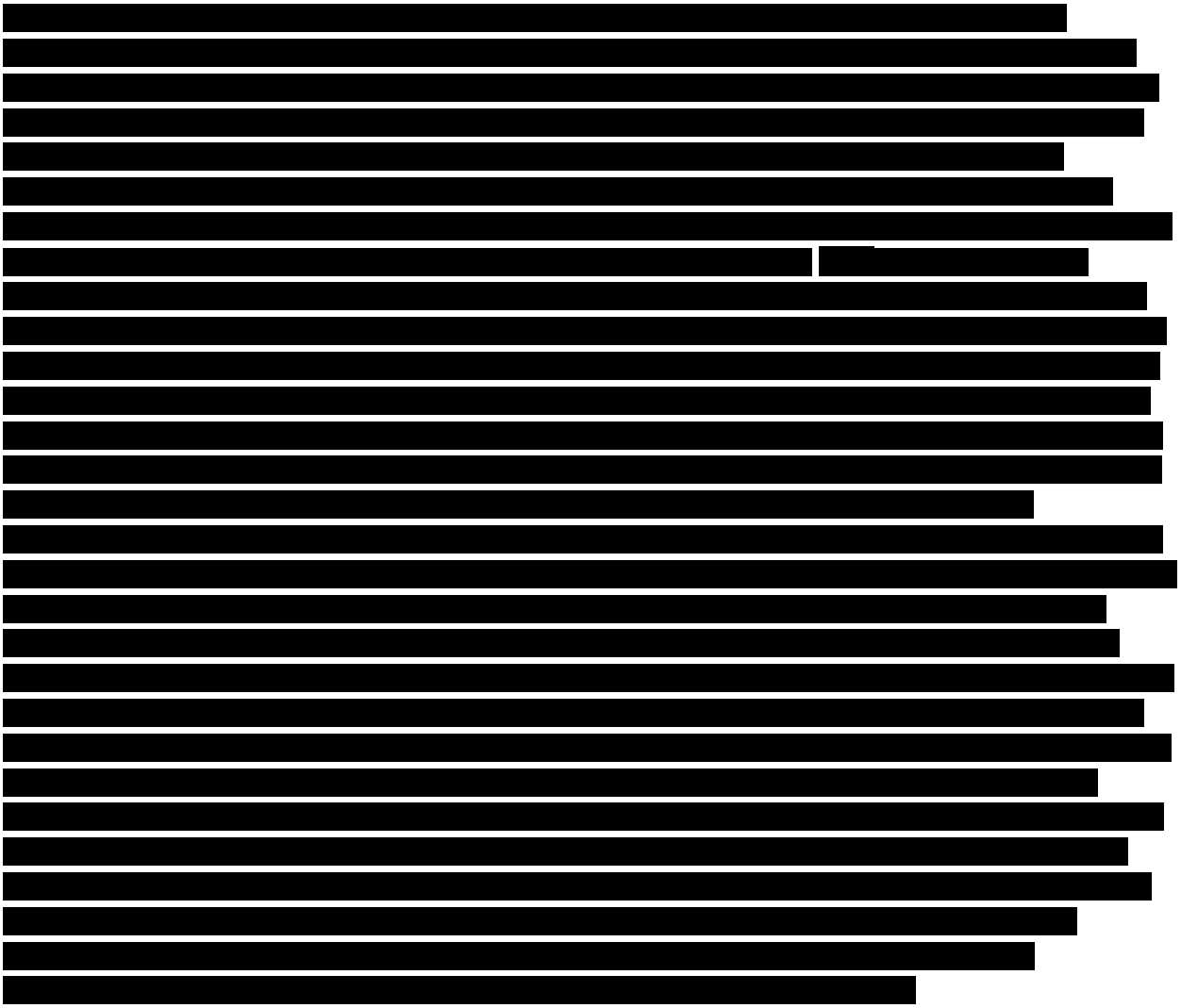
2.5 Exploratory Assessments

2.5.1 Presence of DSAs (mismatched) against all donors

The exploratory analysis is designed to evaluate the prevalence of mismatched subjects within the Randomized Cohort, as well as, the safety and efficacy profiles within the enrolled population. This group of subjects will be called the Exploratory Randomized Cohort. A review and descriptive comparison of safety and efficacy between the Randomized Cohort and the Exploratory Randomized Cohort group will be performed, which preserves the design integrity and statistical power of the Randomized Cohort.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan



In Phase 2, the Primary Randomized Cohort will enroll up to approximately one hundred three (103) subjects with a previous myocardial infarction (MI) and resultant ischemic left ventricular dysfunction meeting all inclusion and no exclusion criteria. The Primary Randomized Cohort will include the Recent and Chronic MI strata. These approximately 103 subjects will be randomized in a double-blind fashion to receive either CAP-1002 or placebo (collectively referred to as Investigational Product [IP]) in a 2:1 ratio favoring CAP-1002 to achieve 93 subjects with complete 12 month data (assumes 10% non-completion rate). Subjects may sign consent and start the screening process immediately post-MI (e.g., acute admission at hospital). The following assessments will be permitted within 28 days immediately following the subject's MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, and platelet count). All other screening tests, including the subject's cardiac MRI and CT (chest, abdomen, pelvis), must be conducted greater than 28 days post-MI. Infusion must occur within 28 days of the first screening procedure that is performed greater than 28 days post-MI. Relevant safety laboratory sample collections (e.g., chemistry, hematology, urinalysis) may need to be repeated as they must be obtained within 28 days of the subject's infusion. A subject that rescreens for any reason may be required to repeat all protocol safety procedures (excluding CT of the chest, abdomen and pelvis if previously conducted) if the safety procedures were originally conducted greater than 28 days prior to the subject's infusion. A subject that rescreens for any reason may be required to repeat all protocol efficacy procedures including the cardiac MRI unless: a) the subject's efficacy procedures including baseline cardiac MRI were conducted within 28 days of infusion; **or**, b) the subject's efficacy procedures including baseline cardiac MRI were conducted **≥** 60 days post-MI **and** within 60 days of infusion. Additional instructions are included in protocol Section 7 and Appendix I (Schedule of Events). After completion of the screening procedures and meeting all inclusion and exclusion criteria, study subjects will be randomized to receive CAP-1002 or placebo administered via intracoronary infusion. All subjects in the Primary Randomized Cohort will be followed at week 2 and at months 1, 3, 6 and 12 after planned CAP-1002 or placebo infusion. Efficacy will be assessed at all specified post-infusion visits, with the 12 month visit being the primary efficacy endpoint. An administrative interim analysis of the final 6 month data will be performed when all subjects in the Primary Randomized Cohort have completed the 6 month visit to assist in planning Phase III studies.

Up to approximately 103 subjects will be enrolled in the Primary Randomized Cohort. This maximum sample size is based on the Recent and Chronic MI strata being analyzed independently with a treatment effect of 15% at Month 12 for each strata, a pooled standard deviation of 10%, a minimum power of 80%, and a significance level (alpha) of 0.05. The double-blind, placebo-controlled design of the Primary Randomized Cohort will maximize the study's ability to assess both safety and efficacy, as both may be subject to bias from the perspective of Investigators and subjects.

The Exploratory Randomized Cohort will enroll up to 17 subjects in addition to the Primary Randomization Cohort. Exploratory Randomized Cohort subjects are those subjects who are mismatched against all available donors. The Exploratory Randomized Cohort will also include Recent and Chronic subjects (up to n=8-9 per stratum). The Exploratory Randomized Cohort will be randomized in a double-blind fashion as described in the Primary Randomized Cohort. The Exploratory Randomized Cohort will undergo the same tests as all other subjects based on the schedule of events (see Appendix 1 Schedule of Events Table). This group will be analyzed

separately from the Primary Randomized Cohort (n=103) using descriptive analyses to assess the prevalence and impact on safety and efficacy, if any. The Exploratory Randomized Cohort sample size was estimated based on DSA results observed in the Safety Cohort, where approximately 14% of the screened subjects would have been mismatched to all available donors, i.e., assuming at 14% rate of mismatch, approximately 120 subjects would be screened to achieve enrollment of 103 in the matched Primary Randomized Cohort, thus yielding up to 17 subjects enrolled in the mismatched Exploratory Randomized Cohort.

3.2 Rationale for Study Design and Control Group

The initial Safety Cohort will provide short term, open label safety data to support both dose escalation to the target dose of 25M cells and continuation into the larger, double-blind portion of the trial. Conducting the Primary Randomized Cohort as double-blind and placebo controlled will maximize the study's ability to assess both safety and efficacy, as both may be subject to bias from the perspective of Investigators and subjects. Adverse events may occur over a 12 month period in subjects with ischemic left ventricular dysfunction regardless of whether or not they receive the study agent. Scoring of these events in terms of the intensity and the relationship to the study therapy can be subject to Investigator bias. Quality of life measures in particular, such as the Six Minute Walk Test, the Minnesota Living with Heart Failure Questionnaire score, SF-36, WPAI-SHP and Patient Global Assessment (some designated as secondary efficacy endpoints), can expose subject bias. Blinding and randomization will serve to help mitigate these potential biases.

3.3 Study Duration and Dates

After the completion of enrollment in the Safety Cohort, it is estimated that 24 months or more of accrual will be necessary to enroll the targeted sample size for the randomized, double-blinded, placebo-controlled portion after a lapse for DSMB review. All treated subjects will be followed for 12 months following infusion. Therefore, the total duration of the study is estimated to be at least 42 months. Actual overall study duration or subject recruitment period may vary. Subjects who sign consent to participate in the 5-year annual follow up (post-infusion) will be followed for an additional 48 months after completing the 12 month post-infusion primary efficacy endpoint visit.

4 STUDY POPULATION SELECTION

4.1 Study Population

Approximately 134 subjects with a history of MI and angioplasty that resulted in a patent infarct-related artery, with stent placement, will be enrolled in this study. These subjects will be primarily recruited from subjects referred to the Principal Investigator at each study site. Of the 134 subjects enrolled, 14 will be part of a Safety Cohort to examine safety of administration of CAP-1002 one month following infusion (followed for 12 months) and up to approximately 103 will be included in the Primary Randomized Cohort. It is anticipated that up to 93 randomized subjects within the Primary Randomized Cohort will complete the study through the 12 month follow up period. The study will enlist approximately 45 sites for participation. Up to 17 additional subjects may be treated as part of the Exploratory Randomized Cohort. However, since this group is exploratory in nature, enrollment of the Primary Randomized Cohort will define the end of the study; that is, once the Primary Randomized Cohort is fully enrolled, the study will be considered closed for further subject enrollment.

4.2 Inclusion Criteria

Subjects meeting the following inclusion criteria may be considered for enrollment:

Inclusion Criteria

1. History of MI (STEMI or NSTEMI) within the prior 12 months due to a coronary artery event and evidenced by at least two of the following: typical ischemic symptoms, serial ST-T changes (new ST elevation or new left bundle block) and/or elevated troponin or CK-MB >5 times the upper limit of normal. Also at least one of the following: development of pathological Q wave ECG changes, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormalities.
    - The following assessments will be permitted within 28 days immediately following the subject's MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, and platelet count). All other screening tests, including the subject's cardiac MRI and CT (chest, abdomen, pelvis), must be conducted greater than 28 days post-MI. Infusion must occur within 28 days of the first screening procedure that is performed greater than 28 days post-MI. Relevant safety laboratory sample collections (e.g., chemistry, hematology, urinalysis) may need to be repeated as they must be obtained within 28 days of the subject's infusion.
2. History of percutaneous coronary intervention (PCI), with stent placement resulting in TIMI flow = 3, in the coronary artery supplying the infarcted, dysfunctional territory and through which the treatment will be infused.
3. At least one assessment of left ventricular ejection function (LVEF) ≤0.45 as determined by any one of the standard modalities (echocardiography, ventriculography, nuclear imaging, CT and/or MRI) prior to or during the screening period.
    - For subjects that fulfill the criteria of Recent MI (i.e., within 90 days of MI) at time of screening visit: assessment must be post-reperfusion after index MI and the most

recent test prior to or during the screening period.
- For subjects that fulfill the criteria of Chronic MI (i.e., greater than 90 days from MI) at the time of screening visit: assessment must be at least 21 days post-reperfusion after index MI and the most recent test prior to or during the screening period.

Note: subjects may screen as a Recent MI but be randomized into the Chronic MI strata if the infusion date is > 90 days post-MI.

4. Left ventricular infarct size of ≥ 15% of left ventricular mass in the qualifying infarct-related region to be infused as determined by centrally read screening MRI, with associated thinning and/or hypokinesis, akinesis, or dyskinesis, with no large aneurysmal area in the infarcted regions.
5. No further revascularization clinically indicated at the time the subject is assessed for participation in the clinical trial.
6. Ability to provide informed consent and follow-up with protocol procedures.
7. Age ≥ 18 years.

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

Exclusion Criteria

1. Subjects with a history of coronary artery bypass surgery, and a patent graft (arterial or saphenous vein graft) attached to the coronary artery to be infused.
2. Diagnosed or suspected myocarditis.
3. History of cardiac tumor, or cardiac tumor demonstrated on screening MRI.
4. History of acute coronary syndrome in the 4 weeks prior to study infusion.
5. History of previous stem cell therapy.
6. History of radiation treatment to the central or left side of thorax.
7. Current or history (within the previous 5 years) of systematic auto-immune or connective tissue disease including, but not limited to, giant cell myocarditis, cardiac or systemic sarcoidosis, Dressler's syndrome, chronic recurrent or persistent pericarditis.
8. History of or current treatment with immunosuppressive , anti-inflammatory, or other agents to treat manifestations of systemic immunologic reactions, including chronic systemic corticosteroids, biologic agents targeting the immune system, anti-tumor and anti-neoplastic drugs, anti-VEGF, or chemotherapeutic agents within 3 months prior to enrollment.
9. Prior ICD and/or pacemaker placement where study imaging site has not been trained and certified specifically for this protocol to conduct cardiac MRI in subjects with ICD and/or pacemaker placement.
    a. Presence of a pacemaker and/or ICD generator with any of the following limitations/conditions are excluded:
        i. Manufactured before the year 2000,
        ii. Leads implanted < 6 weeks prior to signing informed consent,
        iii. Non-transvenous epicardial, abandoned, or no-fixation leads,
        iv. Subcutaneous ICDs,
        v. Leadless pacemakers,
        vi. Any other condition that, in the judgement of device-trained staff, would

deem an MRI contraindicated.

b. Pacemaker dependence with an ICD (Note: pacemaker-dependent candidates without an ICD are not excluded).
c. A cardiac resynchronization therapy (CRT) device implanted < 3 months prior to signing informed consent.

10. Estimated glomerular filtration rate < 30 mL/min.
11. Participation in an on-going protocol studying an experimental drug or device, or participation in an interventional clinical trial within the last 30 days.
12. Diagnosis of arrhythmogenic right ventricular cardiomyopathy.
13. Current alcohol or drug abuse.
14. Pregnant/nursing women and women of child-bearing potential that do not agree to use at least two forms of active and highly reliable method(s) of contraception. Acceptable methods of contraception include contraceptive pills, depo-progesterone injections, a barrier contraceptive such as a condom with or without spermicide cream or gel, diaphragms or cervical cap with or without spermicide or gel, or an intrauterine device (IUD).
15. Human Immunodeficiency Virus (HIV) infection.
16. Viral hepatitis.
17. Uncontrolled diabetes (HbA1c>9%).
18. Abnormal liver function (SGPT/ALT > 3 times the upper reference range) and/or abnormal hematology (hematocrit < 25%, WBC < 3000 µl, platelets < 100,000 µl) studies without a reversible, identifiable cause.
19. Sustained ventricular tachycardia (VT) or non-sustained ventricular tachycardia > 30 beats, not associated with the acute phase of a previous MI (> 48 hours after the MI onset) or a new acute ischemic episode.
20. Ventricular fibrillation not associated with a new acute ischemic episode.
21. New York Heart Association (NYHA) Class IV congestive heart failure.
22. Evidence of tumor on screening chest/abdominal/pelvic (body) CT scan.
23. Any prior transplant.
24. Known hypersensitivity to dimethyl sulfoxide (DMSO).
25. Known hypersensitivity to bovine products.
26. Any malignancy within 5 years (except for in-situ non-melanoma skin cancer and in-situ cervical cancer) of signing the ICF.
27. Any condition or other reason that, in the opinion of the Investigator or Medical Monitor, would render the subject unsuitable for the study.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

CAP-1002 CDCs will be grown from donors unrelated to the recipients. While the HLA type of the recipient subject and the CAP-1002 donor CDCs will be tested and known, primarily for product identification purposes, matching of the donors and subjects will not be performed. Subjects will be assessed for anti-HLA antibodies at screening, but will not be excluded from the study based on the presence of DSAs. Subjects, who can be matched, in the sense that no DSAs are present to one or more donors, will be enrolled in the Primary Randomized Cohort. Subjects, who are mismatched against all available donors, because they harbor one or more anti-HLA antibody against each donor, will be enrolled in the Exploratory Randomized Cohort. Subjects who receive the Investigational Product (IP) (CAP-1002 or placebo) will be monitored during the course of the study for development of increased anti-HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor (i.e. DSAs). The IP is delivered to the clinical sites on an as-needed, per subject basis.

5.1.2 Placebo

Placebo will consist of 11.1 mL of cryopreservation solution (CryoStor® CS10, BioLife Solutions, Inc.) containing 10% dimethyl sulfoxide (DMSO), heparin (1800 units total), and nitroglycerin (450 mcg total).

5.1.3 Wash Solution

Normal saline also containing heparin (1200 units total) and nitroglycerin (600 mcg total) will be used as the intermediate wash solution between boluses of CAP-1002 or placebo. A nitroglycerin-free wash solution may be substituted for the intermediate wash solution if, in the opinion of the operator, the blood pressure is too low for the subject to receive additional nitroglycerin.

5.2 Method of Assigning Subjects to Treatment Groups

Consented subjects will be registered using an Electronic Data Capture (EDC) system. An authorized user at the clinical center completes the initial screening by entering information on the eligibility form. If a Principal Investigator at the study site has any questions regarding subject eligibility, documentation may be directed to the Medical Monitor for consideration.

Subjects in the Safety Cohort received CAP-1002 in an open-label fashion (n=14). In the Randomized Primary and Exploratory Cohorts, all subjects meeting the inclusion and none of the exclusion criteria will be randomized via an interactive web-based system (IWRS) following the screening procedures using an institution balancing algorithm to be deployed using random blocks of 3 or 6 to receive either CAP-1002 or placebo in a 2:1 ratio within stratum, favoring CAP-1002. Subjects that can be matched to receive one or more donors will be randomly assigned to CAP-1002 or placebo (2:1) under the predefined randomization scheme, then subsequently randomized to one of the matched donors. If the subject is mismatched (due to the presence of DSAs) to all available donors, the subject will be randomized to CAP-1002 or placebo (2:1) under the predefined randomization scheme, then randomly assigned to one of the available donors.

Notification of subject randomization will be received by an independent storage/distribution center; the storage/distribution center will have password protected access to the randomization in order to retrieve the treatment assignment. The storage/distribution center will randomly assign an appropriate donor (or placebo) once they receive the designation of active treatment vs. placebo from the IWRS. All Sponsor staff will remain blinded to treatment (CAP-1002 or placebo) assignments as detailed in Section 5.3. The only time other Sponsor staff will become aware of individual treatments is in the case of an emergency blind break resulting from an SAE.

Study sites will be trained regarding the unblinding process. Should a medical event occur necessitating unblinding, the process will be accessible to Investigators 24 hours a day and will include an emergency Sponsor contact.

5.3 Blinding

Subjects will be randomized 2:1 favoring CAP-1002 in a double-blind fashion, with both the Investigators and the subjects blind to treatment received. Central reviewers interpreting the MRI data and the laboratory studies will also be blinded to group assignment.

During the ALLSTAR blinded Primary Randomized Cohort an independent storage/distribution center will be used to distribute IP (CAP-1002 and placebo) doses to the clinical sites. The administration of the blinding process will occur at this independent storage/distribution center to remove Capricor personnel from this process. The distribution and back-up drug product return will occur in validated vapor phase liquid nitrogen (N2) shipping containers allowing for consistent transportation and scheduling flexibility at all sites.

Both CAP-1002 and the placebo will be packaged in identical cryogenic bags with similar labels. At the clinical site, the IP is thawed to room temperature, prepared and drawn into masked (with amber/transparent tape) syringes. The amber/transparent tape will allow the treating physician to see air bubbles but obscure the clear cellular suspension. Specific instructions for use will be included with each product.

A central laboratory will be used to assess the sensitization to products, (i.e., DSAs, ELISpot assay); the results will not be shared with the Investigator or site study personnel or Sponsor staff to preserve blinding.

A DSMB will be utilized for this study and will have access to unblinded data. An interim analysis of the final 6 months data will be completed when subjects complete the 6 month follow-up visit. Only a statistician independent of the clinical trial team will have access to unblinded data and immunological test results prior to the interim analysis; this individual will provide the unblinded reports to the DSMB.

Subjects, investigators, and Sponsor's personnel who had direct responsibility for monitoring at the sites will be blinded throughout the study. The interim analysis will be considered an administrative interim analysis planned for the determination of efficacy at 6 months, the appropriate Sponsor representatives will be unblinded in order to review and make decisions regarding entry into Phase III clinical development. A list will be maintained in the trial master file to track any persons unblinded during the trial.

Study sites will be trained regarding the emergency unblinding process. Should a medical event occur necessitating unblinding, the process will be accessible to Investigators 24 hours a day and will include an emergency Sponsor contact.

It is not believed that unblinding would help in the treatment of the subjects participating in the study. However, if a medical event should occur which necessitates emergency unblinding; the process will be accessible to Investigators 24 hours a day. Study sites will be trained regarding the emergency unblinding process.

5.4 Concomitant Therapy

All medication therapies received from the time of signing consent will be collected. These are considered concomitant therapies. Concomitant therapies will be recorded at each study visit, beginning with Screening. All subjects will receive standard-of-care for their cardiac condition as determined by their cardiologist. Immunosuppressive, anti-inflammatory, or other agents used to treat systemic immunologic reactions, including chronic systemic corticosteroids, anti-tumor and anti-neoplastic drugs, anti-VEGF, biologic agents targeting the immune system and chemotherapeutic agents are prohibited; subjects taking any of these medications within 3 months prior to the study infusion are prohibited from participation in the study. Appendix 2 provides a list of prohibited medications. However, if a subject is started on one of these medications following the IP infusion, they will be allowed to continue in the study.

5.5 Restrictions

5.5.1 Prior Therapy

Subjects who have had previous stem cell therapy, or central or left thorax radiation may not participate in this study.

There are no medication restrictions except those listed in Section 5.4 and Appendix 2. Individual subject medication will be advised by the subject's physician according to the usual practice of the study site. Warfarin (Coumadin®) discontinuation prior to catheterization will be

managed according to the practice and standards of the study site.

5.5.2 Fluid and Food Intake

There are no fluid or food intake restrictions. Subjects should follow the diet and fluid intake prescribed by their physician.

5.5.3 Subject Activity Restrictions

Subjects should follow the activity restrictions prescribed by their physician.

5.6 Treatment Compliance

Since the treatment is a one-time procedure (i.e., infusion), dosing compliance is not of concern. Study site personnel will document use of all concomitant medications and subject compliance with study procedures at each study visit.

5.7 Packaging and Labeling

CAP-1002 and the placebo will be formulated and frozen in labeled cryogenic bags with 510K approval for the use in protecting, storing and freezing cells and tissues. A cryogenic overwrap bag will be used to protect the cryogenic bag and label during freezing. Labeling will be attached to the cryogenic overwrap bag for quick identification. The storage/distribution center will distribute the IP (which may include a back-up IP at instruction of the Sponsor) to the clinical sites using a validated vapor phase liquid N2 shipping containers. The unused back-up IP, as applicable, will be returned to the storage/distribution center using the same shipping container.

5.8 Storage and Accountability

CAP-1002 (or placebo) will be shipped to sites as needed on an individual subject basis and only after a subject has (1) provided written informed consent, (2) met all eligibility criteria for entry into the study, (3) successfully completed all screening evaluations and 4) been randomized to receive either CAP-1002 or placebo treatment. The investigational products will not be stored at individual sites other than in the shipping materials provided by the Sponsor.

Detailed instructions for storage and handling are provided in the Instructions for Use that are included with each individual treatment shipment. Sites are instructed to hold the IP in its shipping container until it is dispensed just prior to infusion. The Sponsor will time delivery of the IP to the clinical sites such that the time in the shipping container is less than the known expiration time. **Once removed from the shipping container, the IP expires at 90 minutes post-removal.** An expiration time will be noted on the product at the time of removal and preparation. Investigators are instructed to store the IP at room temperature (approximately 25°C) and to administer the IP prior to the noted expiration time.

5.9 Investigational Product Retention at Study Site

Since IP will be delivered as needed on a per subject basis, there will be no IP to retain at the site. Site will be instructed to retain labels and packaging materials as part of the subject records. Should a subject be found unsuitable for infusion after IP has been shipped, the site is instructed to return the IP to the Sponsor's Manufacturing Facility per the Sponsor's instructions.

5.10 Investigational Product Accountability and Reconciliation

The Sponsor is responsible for IP accountability, reconciliation, and record maintenance. Training will be provided regarding IP accountability. In accordance with all applicable regulatory requirements, the designated study center personnel must maintain accountability records throughout the study, and the Sponsor (or, designee) will review IP accountability and reconciliation.

6 STUDY PROCEDURES

6.1 Informed Consent

Before being admitted to the clinical study, all subjects must consent in writing to participate. An Informed Consent Form (ICF) will be given to each subject, which will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the subject. The process of obtaining the informed consent will be in compliance with all federal regulations, International Conference on Harmonisation (ICH) requirements, and local laws. Per this protocol, the subject may sign the ICF immediately post-MI (e.g., acute admission at hospital). The following assessments will be permitted within 28 days immediately following the subject's MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, and platelet count). All other screening tests, including the subject's cardiac MRI and CT (chest, abdomen, pelvis), must be conducted greater than 28 days post-MI. Infusion must occur within 28 days of the first screening procedure that is performed greater than 28 days post-MI. Relevant safety laboratory sample collections (e.g., chemistry, hematology, urinalysis) may need to be repeated as they must be obtained within 28 days of the subject's infusion. Additional instructions are included in protocol Section 7 and Appendix I (Schedule of Events).

The Investigator and/or designee must discuss the study with each subject. The discussion will include the nature, scope, procedures, and possible consequences of the subject's participation in the study. The ICF and review will be in a form understandable to the subject. The subject must be given adequate time to review the ICF and ask questions regarding the IP, procedures, risks and other treatment. The Investigator or designee and the subject must both sign and date the ICF after review and before the subject can participate in the study. The subject will receive a copy of the signed and dated form, and the original will be retained in the site study files. The Investigator or his/her designee will emphasize to the subject that study participation is entirely

voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The site must use the amended consent form for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

6.2 Medical History

The general and cardiac-specific medical histories (e.g., significant procedures, medications, therapies, allergies) of subjects enrolled in the study will be documented as part of the screening visit and reviewed during subsequent visits (e.g., day of infusion, follow-up visits) for any modifications (i.e., assessment for potential adverse events). General and cardiac health, as well as concomitant medications, will be reviewed and assessed at each subject visit and new information will be updated in the subject's study documentation.

6.3 Physical Examinations

A qualified physician, either the Investigator or Sub-Investigator, will perform a limited cardiovascular physical examination at each study visit which will include angina and arrhythmia assessments.

A limited physical examination will be conducted at the screening visit and the 12 Month follow-up visit. Height and weight will also be collected and recorded at screening; weight will be collected at all subsequent visits.

6.4 Vital Signs

Temperature, heart rate, blood pressure and respiration rate will be recorded at each visit on the case report form.

6.5 Clinical Laboratory Tests

6.5.1 Laboratory Parameters

Section 7 and Appendix I (Schedule of Events) list applicable clinical laboratory tests to be collected at study visits. Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests will include the following:

Table 1. List of Laboratory Tests

Hematology:
Hematocrit (Hct)
Hemoglobin (Hgb)
Platelet count
White blood cell (WBC) count with differential

Urinalysis:
Appearance
Bilirubin
Color Glucose Ketones
Microscopic examination of sediment
Nitrite
Occult blood pH
Protein
Specific gravity
Urobilinogen

Serum beta human chorionic gonadotropin (hCG) (only for females who are not diagnosed as postmenopausal)

Donor Specific Antibody (DSA) monitoring and HLA (Human Leukocyte Antigen) typing

ELISpot assay

Serum Biomarkers (if subject provided consent)

Serum Chemistry:
Alanine aminotransferase (ALT; SGPT)
Aspartate aminotransferase (AST; SGOT)
Blood urea nitrogen (BUN)
Creatinine
Estimated Glomerular filtration rate (eGFR)
Glucose
Lactate dehydrogenase (LDH)
Potassium (K)
Sodium (Na)

Hemoglobin A1c (HbA1c) (screening)

Troponin I or Troponin T if Troponin I is not available.
N-terminal pro-hormone brain natriuretic peptide (NT-proBNP)

Coagulation [Infusion Visit only - for subjects taking warfarin (Coumadin®)]:

Activated partial thromboplastin time(PTT)
International Normalized Ratio (INR)

Hepatitis B surface Antigen (HBsAg) (screening)
Hepatitis C Virus (HCV) (screening)
Human Immunodeficiency Virus (HIV) (screening)

6.5.2 Sample Collection, Storage, and Shipping

Laboratory studies will be performed and reported at each individual study site, with the exception of the following:

Serum for the donor specific antibody (DSA) monitoring, HLA typing and blood for the ELISpot assay will be collected and processed at each site and then shipped to a central core laboratory for analysis within 24 hours of obtaining the specimens (See Laboratory Manual for shipping instructions). Subjects will be monitored for the development of a cellular immune response using the ELISpot (enzyme-linked immunosorbent spot) assay. The ELISpot assay will be performed at screening and at the one month study visit in a total of 50 patients treated with CAP-1002 (and concurrently 18 placebo subjects: 14 open-label CDC subjects, 36 randomized CDC subjects, 18 randomized placebo subjects) and will be reviewed by the DSMB. If the DSMB determines that there is reason to believe additional value would be gained from a larger sample of subjects, ELISpot testing will be performed for additional subjects, followed by additional, subsequent DSMB review.

- Serum for research purposes (biomarkers) will be collected and processed at each site then shipped to a central core lab that will then ship to Capricor for final storage and analysis (if subject has provided consent).

Individual sites will be instructed regarding the processing and shipping procedures.

6.6 12-Lead ECG

Beginning at the screening visit, a 12-Lead ECG will be performed at every study visit to assess for rhythm disturbances and new myocardial ischemia or infarction. Subsequent ECGs will be compared with the screening ECG for any changes in rhythm and conduction. All changes and any associated clinical significance will be evaluated and documented on the case report forms.

6.7 Echocardiography

An echocardiogram will be performed at the screening visit as well as the 1 month visit. Echocardiography will be performed to measure the size and shape of the heart, its chambers and blood flow as well as valvular structure and function. Additionally, the echocardiogram will be used for detection of any wall motion abnormalities indicative of myocarditis.

The quantitative echocardiographic data points must include:

- End Diastolic Volume
- End Systolic Volume
- Ejection Fraction
- LV End Systolic Diameter
- LV End Diastolic Diameter

6.8 24 Hour Ambulatory ECG Monitor

A 24 hour ambulatory ECG monitor will be performed at the screening visit, during the 24 hours following release (discharge) from the hospital and also at the 1 month, 6 months and 12 months study visits. Subjects enrolled in the Safety Cohort will also have the test performed at the 2 months study visit. The monitor is used to detect and record arrhythmia. All changes and any associated clinical significance will be evaluated and documented on the case report form.

6.9 Magnetic Resonance Imaging Protocol

With the exception of those subjects who develop MRI contraindications, all subjects will undergo contrast-enhanced MRI at screening and the months 6 and 12 study visits. Study imaging sites must be trained and certified specifically for this protocol prior to conducting cardiac MRI in subjects with ICD and/or pacemaker placement. The imaging protocol will first include sagittal, axial and oblique scout images to localize the heart. It is anticipated that the duration of each MRI session will be 45-60 minutes. Acquisition parameters and techniques will be protocoled and the site-based MRI technicians will be trained and certified in the common acquisition protocol prior to initiation of enrollment at each site.

6.9.1 Cine Imaging Protocol

A cine imaging protocol will be utilized for global ejection fraction and LV volumes and mass determination. Acquisition parameters and techniques will be protocoled and the site-based MRI technicians will be trained and certified in the common acquisition protocol prior to initiation of enrollment at each site.

6.9.2 Delayed Contrast-Enhancement Protocol

This is the most accurate assessment of infarct scar size. Subjects will receive a total bolus intravenous injection of 0.2 mmol/kg of gadolinium contrast as long as GFR is > 60 mL/min (for GFR 30-60 mL/min, 0.15 mmol/kg will be given; subjects whose GFR declines to <30 during the study period will be excluded from contrast injections during subsequent MRI studies). High-resolution delayed enhancement images will be obtained using an inversion- recovery prepared gated fast gradient echo pulse sequence.

6.9.3 Image Analysis

All study images and applicable imaging data will be sent to and centrally read at an independent imaging core by cardiovascular radiology experts. MRI will be performed on standard phantoms for quality assurance and to detect any changes in system sensitivity over time.

6.10 Chest, Abdomen and Pelvis CT

A computerized tomography (CT) of the chest, abdomen and pelvis will be performed at the screening visit to ensure that there are no clinically significant pre-existing abnormalities to internal organs or presence of tumors or cancer. The CT will be performed with contrast. If any

abnormalities are found that affect the subject's participation in the study, the subject will be withdrawn from the study as a screen failure and not followed further. The subject must continue to meet all inclusion and no exclusion criteria in order to continue in the study.

6.11 Clinical Function and Quality of Life Measures

At the screening, 6 month and 12 month study visits, the subject will be asked to complete the Minnesota Living with Heart Failure Questionnaire (MLHFQ), the Short Form-36 health survey (SF-36), the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), and to make a global assessment of the improvement or worsening of his/her condition (Patient Global Assessment).

In addition, subjects will perform a Six Minute Walk test at screening, and at the 6 and 12 month study visits. New York Heart Association (NYHA) functional status will be evaluated at screening, 1 month, 3 months, 6 months and 12 months study visits.

7 STUDY ACTIVITIES

The Schedule of Events for the conduct of this study is shown in Appendix 1.

Subjects may sign consent and start the screening process immediately post-MI (e.g., acute admission at hospital). The following assessments will be permitted within 28 days immediately following the subject's MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, and platelet count). All other screening tests, including the subject's cardiac MRI and CT (chest, abdomen, pelvis), must be conducted greater than 28 days post-MI. Infusion must occur within 28 days of the first screening procedure that is performed greater than 28 days post-MI. Relevant safety laboratory sample collections (e.g., chemistry, hematology, urinalysis) may need to be repeated as they must be obtained within 28 days of the subject's infusion. A subject that rescreens for any reason may be required to repeat all protocol safety procedures (excluding CT of the chest, abdomen and pelvis if previously conducted) if the safety procedures were originally conducted greater than 28 days prior to the subject's infusion. A subject that rescreens for any reason may be required to repeat all protocol efficacy procedures including the cardiac MRI unless: a) the subject's efficacy procedures including baseline cardiac MRI were conducted within 28 days of infusion; **or**, b) the subject's efficacy procedures including baseline cardiac MRI were conducted ≥ 60 days post-MI **and** within 60 days of infusion. After completion of the screening procedures and meeting all inclusion and exclusion criteria, study subjects will be randomized to receive CAP-1002 or placebo administered via intracoronary infusion. Study subjects will undergo catheterization and infusion on the day of admission and will be observed in the hospital with continuous cardiac monitoring overnight, 20 to 24 hours afterwards. In the absence of serious adverse events, subjects will be discharged the day after catheterization, with a 24-hour ambulatory ECG monitor.

7.1 Screening Period

No screening exams will take place until the subject is fully informed of the research and signs the informed consent. Subjects may sign consent and start the screening process immediately post-MI (e.g., acute admission at hospital). The following assessments will be permitted within 28 days immediately following the subject's MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, and platelet count). All other screening tests, including the subject's cardiac MRI and CT (chest, abdomen, pelvis), must be conducted greater than 28 days post-MI. Relevant safety laboratory sample collections (e.g., chemistry, hematology, urinalysis) may need to be repeated as they must be obtained within 28 days of the subject's infusion.

Screening tests and procedures include:

- Medical history, limited physical examination, and cardiac physical examination
- Medication review
- Vital Signs
- 12-Lead ECG
- Laboratory tests: HLA typing, DSA evaluation
- Echocardiography
- Cardiac MRI
- Laboratory tests: hematology, chemistry, urinalysis, hemoglobin A1c (HbA1c), serum NT-proBNP, Serum β- HCG (only for females who are not diagnosed as postmenopausal), HIV and hepatitis screens, ELISpot Assay sample; refer to Table 1 for comprehensive list of laboratory tests
- Serum for biomarkers (if subject has provided consent)
- 24 hour ambulatory ECG monitoring
- NYHA functional class assessment
- Six Minute Walk Test
- MLHFQ
- SF-36 health survey
- WPAI:SHP questionnaire
- Patient Global Assessment
- Adverse event assessment
- CT of the chest, abdomen and pelvis [note: the subject's CT of the chest, abdomen, and pelvis should be conducted after all other screening study eligibility criteria have been met, including independent imaging core confirmation of baseline (screening) MRI eligibility]

A subject that rescreens for any reason may be required to repeat all protocol safety procedures (excluding CT of the chest, abdomen and pelvis if previously conducted) if the safety procedures were originally conducted greater than 28 days prior to the subject's infusion. A subject that rescreens for any reason may be required to repeat all protocol efficacy procedures including the

cardiac MRI unless: a) the subject's efficacy procedures including baseline cardiac MRI were conducted within 28 days of infusion; **or**, b) the subject's efficacy procedures including baseline cardiac MRI were conducted ≥ 60 days post-MI **and** within 60 days of infusion.

Protocol safety procedures are defined as:

- Medical history, limited physical examination, and cardiac physical examination
- Medication review
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, hemoglobin A1c (HbA1c), serum NT- proBNP, Serum β- HCG (only for females who are not diagnosed as postmenopausal), HIV and hepatitis screens, and serum for biomarkers (if subject has provided consent); refer to Table 1 for comprehensive list of laboratory tests
- 24 hour ambulatory ECG monitoring
- Adverse event assessment

Protocol efficacy procedures are defined as:

- Laboratory tests: serum NT- proBNP HLA typing, DSA evaluation, ELISpot Assay sample
- Echocardiography
- Cardiac MRI
- NYHA functional class assessment
- Six Minute Walk Test
- MLHFQ
- SF-36 health survey
- WPAI:SHP questionnaire
- Patient Global Assessment

Randomization will occur after all of the screening examinations have been completed and only if the subject continues to meet all of the eligibility criteria. After the subject is randomized, the subject must continue to meet eligibility criteria before proceeding to intracoronary infusion. Sites should randomize eligible subjects at least three (3) working days ***prior*** to a subject's scheduled infusion date. The Sponsor should be notified of cases that prevent randomization at least three (3) working days prior to a subject's scheduled infusion date (e.g., timing of MRI results). Subjects who are not randomized and do not proceed to infusion due to violation of eligibility criteria at screening will be withdrawn from the study as screen failures and will have no further follow up.

7.2 Treatment Period

7.2.1 Intracoronary Infusion Visit (Day 0)

Intracoronary infusion of CAP-1002 or placebo must occur within 28 days of the first screening procedure that is performed greater than 28 days post-MI. At the infusion visit, subjects will be clinically stable as judged by no evidence of infection, stable blood pressure and pulse, as well as over the prior four days by history no change in angina pattern, or in angina or heart failure medications.

As part of the infusion visit, subjects will undergo the following tests and assessments:

Pre-infusion:

- Medical history and cardiac physical examination
- Medication review
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, serum NT-proBNP, and INR/PTT [as needed for subjects on warfarin (Coumadin®)]; refer to Table 1 for comprehensive list of laboratory tests
- Cardiac enzymes (Serum troponin and CK-MB)

Post-infusion:

- Cardiac assessment
- Vital signs approximately every 8 hours (from infusion time) until discharge
- Cardiac enzymes (serum troponin and CK-MB) approximately every 8 hours x3 with last blood draw immediately prior to discharge (20-24 hours post infusion)
- Urinalysis
- 12-Lead ECG (day of discharge)
- 24 hour ambulatory ECG monitoring (apply to subject immediately prior to discharge)
- Adverse Event assessment

Subjects must have a patent coronary artery with TIMI flow 3 in order for the IP to be infused. Subjects with angiographic evidence of a coronary occlusion determined to be clinically significant, with or without clinical symptoms during the day of IP infusion: 1) will not undergo intracoronary infusion of the IP, 2) will be withdrawn from the study, and 3) will not be followed further for either safety or efficacy. The decision to attempt opening and restoration of TIMI-3 flow will be based on clinical grounds.

Stopping criteria that would trigger halting of the CAP-1002 or placebo infusion are:

1. Sustained hypotension unresponsive to fluids and/or medications.
2. Evidence of acute coronary syndrome.
3. Development of TIMI flow 0/1, after a cycle of infusion.
4. Evidence of cerebrovascular accident.
5. Evidence of cardiac tamponade.
6. Hemopericardium requiring pericardiocentesis.
7. Sustained ventricular tachycardia/ventricular fibrillation that require cardioversion or administration of an antiarrhythmic.
8. Evidence of thrombus in the aorta that was not previously seen on imaging studies.
9. Suspected or confirmed aortic dissection.
10. Suspected or confirmed coronary dissection.

11. Acute onset of rigors (symptoms indicative of acute sensitivity or infection).
12. Sustained ST-segment elevation or angina symptoms which persist longer than the time the balloon is deflated (> 3 minutes) with angiographic evidence of microvascular obstruction (i.e., no reflow).

Following intracoronary infusion, subjects will be observed in the hospital for 20-24 hours with continuous cardiac (telemetry) monitoring. Troponin and CK-MB laboratory studies will be monitored every 8 hours from the end of the infusion. A total of three sets of cardiac enzymes will be evaluated to rule out cardiac injury during the post-infusion hospital stay through discharge. If the subject is discharge prior to 24 hours, cardiac enzymes will be drawn just prior to discharge.

Prior to discharge from the hospital, a physical assessment will be performed which will include chest pain assessment, review of laboratory results, ECG, and arterial puncture site as well as assessment of adverse events. In the absence of serious adverse events, subjects will be discharged the day after infusion with a 24 hour ambulatory ECG monitor.

The timing of follow-up visits is based on the date of actual or planned IP administration. Following intracoronary infusion, a subject visit schedule listing target dates for assessments can be printed from the EDC system.

7.2.2 Intracoronary Infusion Procedure

All subjects will receive a dose of IP suspended in 11.1mL of cryopreservation solution (CryoStor® CS10, BioLife Solutions, Inc. containing 10% DMSO, 1800 units heparin and 450 mcg nitroglycerin). Twelve milliliters of an intermediate wash solution containing saline, 1200 units heparin and 600 mcg nitroglycerin is also administered to each subject between boluses of CAP-1002 or placebo. **A nitroglycerin-free wash solution may be substituted for the intermediate wash solution if, in the opinion of the operator, the blood pressure is too low for the subject to receive additional nitroglycerin.** See Table 2 for total heparin and nitroglycerin for infusion/wash scenarios.

Intracoronary infusion of the IP will be performed using the Abbott Trek® "over the wire" (OTW) balloon angioplasty catheter. A balloon catheter up to 0.5 mm larger in diameter than the stent diameter and shorter in length (preferably 8-12 mm) will be positioned in the stented segment and inflated at pressures to achieve occlusion of blood flow in the infarct- related artery; this is to prevent reflux of the IP infusion. The IP will then be injected through the wire lumen of the balloon catheter after the guide wire is removed. The balloon is kept inflated for approximately 2 minutes 15 seconds and deflated for approximately 3 minutes in 3 cycles for a total procedure time of approximately 12 minutes 45 seconds. Exact balloon inflation and deflation times as well as exact infusion times will be recorded during the procedure.

One third of the 11.1mL total volume of IP is infused as a bolus during each balloon inflation cycle over the course of approximately 1 minute and 45 seconds. Two mL of the wash solution are infused before the IP bolus and 2 mL of the wash solution are infused after each IP bolus, both over the course of approximately 15 seconds, so as to wash any remaining IP solution from

the catheter (see Figure 1). Subjects may be given intravenous fluids and medications as necessary for hypotension during the procedure, per the Investigator's discretion.

Epicardial coronary flow and myocardial perfusion will be assessed quantitatively at the beginning and at the completion of the infusion procedure, using the validated TIMI flow score. However, if ST elevation or angina symptoms persist after 3 minutes with the balloon deflated, a diagnostic contrast injection will be performed and TIMI flow will be assessed. If ECG abnormalities and/or symptoms are due to impairment of blood flow at the myocardial level (microvascular obstruction), cell infusion will be terminated.

Hemodynamics, symptoms, and electrocardiogram are continuously monitored while subjects are in the catheterization laboratory. If there is any evidence of infarction, the infusion protocol will be halted. Subjects will be monitored for 20 - 24 hours following the infusion, including a detailed physical examination for evidence of neurologic dysfunction and bleeding, as well as ECG and cardiac enzymes for arrhythmias and cardiac damage.

Figure 1. Schematic of Infusion Protocol

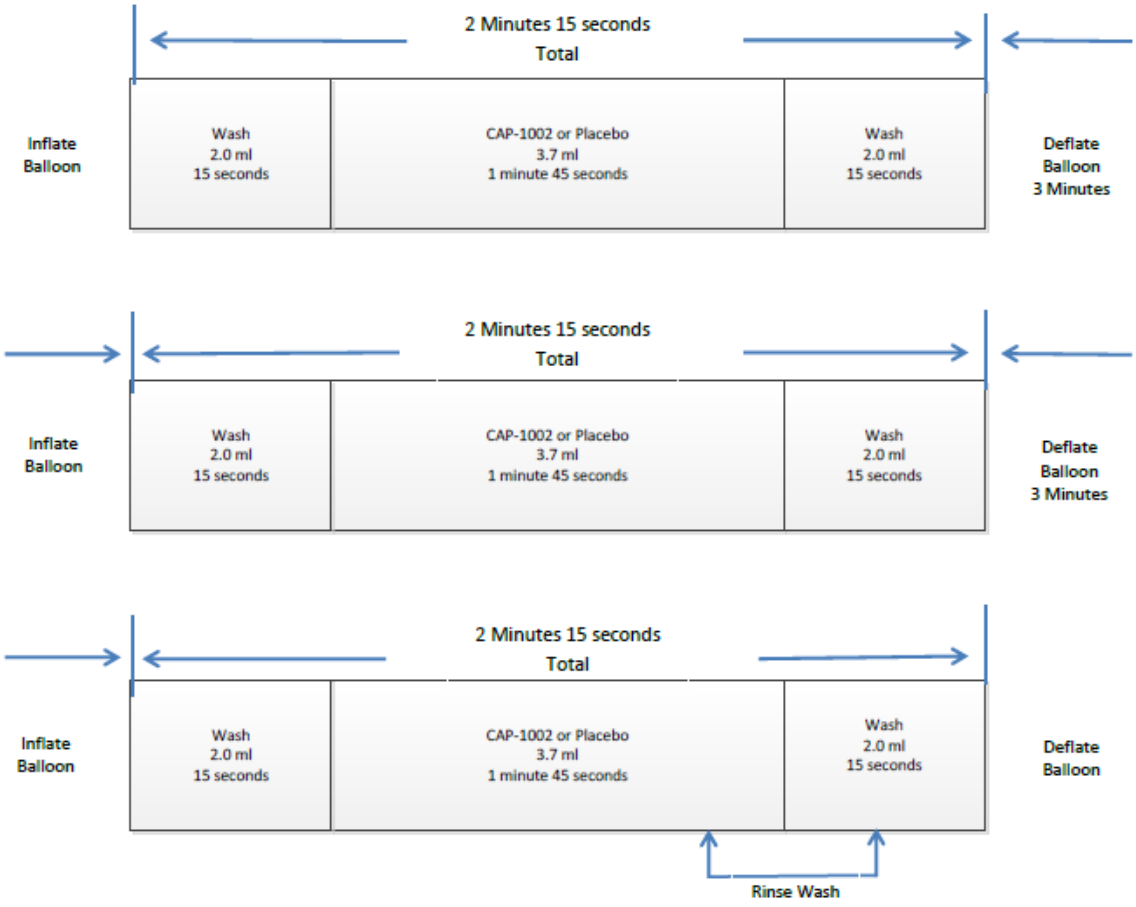


Table 2. Infusion Scenarios for Nitroglycerin and Heparin Doses

	CAP-1002 vs. Placebo		**Bolus 1**		**Bolus 2**		**Bolus 3**		**Total doses**	
	Heparin (U)	NTG (mcg)	Heparin (U)	NTG (mcg)	Heparin (U)	NTG (mcg)	Heparin (U)	NTG (mcg)	Heparin (U)	NTG (mcg)
Scenario #1 **NTG free wash** with **all** bolus'	1800	450	400		400		400		**3000**	**450**
Scenario #2 **NTG free wash** with **2 of 3** bolus'	1800	450	400	200	400		400		**3000**	**650**
Scenario #3 **NTG free wash** with **1 of 3** bolus'	1800	450	400	200	400	200	400		**3000**	**850**
Scenario #4 **NTG Wash with all bolus'**	1800	450	400	200	400	200	400	200	**3000**	**1050**

7.3 Follow-Up Period

7.3.1 Week 2 Visit (Day 14 ± 3 days) Procedures

The following procedures will be performed at the Week 2 visit:

- Cardiac physical examination
- Medication review
- Adverse events assessment
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, DSA monitoring, serum NT-proBNP, measurement of cardiac enzymes (serum troponin and CK-MB); *refer to Table 1 for comprehensive list of laboratory tests*
- Serum for biomarkers (if subject has provided consent)

7.3.2 Month 1 Visit (Day 30 ± 3 days) Procedures

The following tests and procedures will be performed at the one month visit:

- Cardiac physical examination
- Medication review
- Adverse events assessment
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, DSA monitoring, and ELISpot assay, serum NT-proBNP, measurement of cardiac enzymes (serum troponin and CK-MB); *refer to Table 1 for comprehensive list of laboratory tests*
- 24 hour ambulatory ECG recording
- Echocardiography
- NYHA functional class assessment

Echocardiography, as mandated in the protocol, will be performed to rule out any new regional or global myocardial dysfunction, possibly secondary to inflammation. Cardiac biopsy may be performed at any point during the study if clinically indicated by the currently accepted recommendations based on expert consensus (Cooper, 2009). If myocarditis is diagnosed by histopathologic or clinical criteria, it will be treated according to current standard-of-care. Causes of myocarditis that are not likely related to study therapy may include: viral infection, bacterial infection, protozoal infection, toxins, drugs, autoimmune diseases, giant cell myocarditis, and sarcoidosis (Blauwet & Cooper, 2010).

7.3.3 Month 2 Visit (Day 60 ± 6 days) Procedures (Phase I Safety Cohort Only)

The month 2 visit will be performed for Phase I Safety Cohort subjects only.

At the two-month visit the following tests and procedures will be performed:

- History and cardiac physical examination
- Medication review
- Adverse events assessment
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, DSA monitoring, serum NT-proBNP; refer to Table 1 for comprehensive list of laboratory tests
- Serum for biomarkers (if subject has provided consent)
- 24 hour ambulatory ECG recording
- NYHA functional class assessment

7.3.4 Month 3 Visit (Day 90 ± 6 days) Procedures

At the three-month visit the following tests and procedures will be performed:

- Cardiac physical examination
- Medication review
- Adverse events assessment
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, DSA monitoring, serum NT-proBNP; refer to Table 1 for comprehensive list of laboratory tests
- Serum for biomarkers (if subject has provided consent)
- NYHA functional class assessment

7.3.5 Month 6 Visit (Day 180 ± 6 days) Procedures

Subjects will undergo multiple assessments 6 months after intracoronary infusion, including:

- Cardiac physical examination
- Medication review
- Adverse events assessment
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, DSA monitoring, serum NT-proBNP; refer to Table 1 for comprehensive list of laboratory tests
- Serum for biomarkers (if subject has provided consent)

- Cardiac MRI
- 24 hour ambulatory ECG recording
- NYHA functional class assessment
- Six Minute Walk Test
- MLHFQ
- SF-36 health survey
- WPAI:SHP questionnaire
- Patient Global Assessment

If subjects undergo inter-current ICD/pacemaker placement, study imaging sites must be trained and certified specifically for this protocol prior to conducting cardiac MRI in subjects with ICD and/or pacemaker placement. If subjects develop MRI contraindications, a cardiac MRI will not be performed. Such subjects will continue to be followed in the study and undergo all 6 month study procedures except MRI. Any subject whose GFR declines to <30 mL/min during a given MRI study will not undergo contrast administration on this and subsequent MRI studies. Such treated subjects will not be withdrawn but will still be followed for inclusion in safety and efficacy analyses for other parameters assessed during the study.

7.3.6 Month 12 Visit (Day 360 ± 6 days) Procedures

Subjects will undergo multiple assessments 12 months after intracoronary infusion, including:

- Limited physical examination and cardiac physical examination
- Medication review
- Adverse events assessment
- Vital signs
- 12-Lead ECG
- Laboratory tests: hematology, chemistry, urinalysis, DSA monitoring, serum NT-proBNP; refer to Table 1 for comprehensive list of laboratory tests
- Serum for biomarkers (if subject has provided consent)
- Cardiac MRI
- 24 hour ambulatory ECG recording
- NYHA functional class assessment
- Six Minute Walk Test
- MLHFQ
- SF-36 health survey
- WPAI:SHP questionnaire
- Patient Global Assessment

If subjects undergo inter-current ICD/pacemaker placement, study imaging sites must be trained and certified specifically for this protocol prior to conducting cardiac MRI in subjects with ICD and/or pacemaker placement. If subjects develop MRI contraindications, a cardiac MRI will not be performed. Such subjects will continue to be followed in the study and undergo all 12 month

study procedures except MRI. Any subject whose GFR declines to <30 mL/min during a given MRI study will not undergo contrast administration on this and subsequent MRI studies. Such treated subjects will not be withdrawn but will still be followed for inclusion in safety and efficacy analyses for other parameters assessed during the study.

7.3.7 Annual Follow-up Phone Call

With consent of the subject, following completion of the 12 Month Visit or following early withdrawal, all enrolled subjects who completed treatment infusion will be contacted by phone annually on the anniversary of their infusion (± 2 weeks) through year 5 (post-infusion) to assess for Major Adverse Cardiac Event (MACE), defined as the composite incidence of death, non-fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant.

7.4 Performing Adverse Events Assessments

An Adverse Event (AE) is any untoward medical occurrence in a subject or clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The occurrence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition.
- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- A new condition detected or diagnosed after study therapy administration even though it may have been present prior to the start of the study.
- Pre- or post-treatment events that occur as a result of protocol-mandated procedures (e.g., invasive protocol-defined procedures, modification of a subject's previous treatment regimen).

An AE does <u>not</u> include:

- Medical or surgical procedures (e.g., colonoscopy, biopsy). The medical condition that leads to the procedure is an AE.
- Social or convenience hospital admissions where an untoward medical occurrence did not occur.
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe than expected for the subject's condition.

The Investigator will review all documentation (e.g., hospital progress notes, laboratory, or

diagnostic reports) relative to the event being reported. The Investigator will then record all relevant information regarding an AE/SAE into the electronic data system. It is not acceptable for the Investigator to send photocopies of the subjects' medical records in lieu of completion of the appropriate AE/SAE pages. However, there may be instances when UBC Safety requests copies of medical records for certain cases. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to UBC Safety.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs and symptoms.

Adverse events classified by the Investigator as related to investigational product or the administration procedure, potential safety endpoints and MACEs are adjudicated by the Clinical Endpoints Committee (CEC). Detailed information on the CEC adjudication process can be found in the Clinical & Adverse Event Reporting & Adjudication Procedures Manual.

7.4.1 Timing

Adverse event assessment and documentation will occur at every study visit from screening throughout the study. On the day of treatment administration, a subject's medical complaint will be considered to be a treatment-emergent adverse event if the event occurs any time after the time vascular access is obtained at the beginning of the catheterization for the infusion of CAP-1002 (or placebo).

7.4.2 Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgment. The intensity of each AE and SAE will be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is described as 'serious' when it meets one of the pre-defined outcomes as described in the Section 7.4.7 Serious Adverse Events.

7.4.3 Relationship

The Investigator is obligated to assess the relationship between study therapy and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the pharmacological action of the study agent was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases, concomitant

therapy, other risk factors, and the temporal relationship of the event to the study agent will be considered and investigated. The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

All AE/SAE that occur during the course of the clinical study will be evaluated and a determination of relatedness to the investigational product or procedure will be defined according to one of the following categories:

- Definite: The AE/SAE is clearly related to the investigational product or procedure.
- Probable: The AE/SAE is likely related to the investigational product or procedure.
- Possible: The AE/SAE may be related to the investigational product or procedure. All AEs and SAEs that occur within 24 hours of intervention will, because of the temporal relationship, be considered as at least possibly related to the investigational product or procedure and will be reported to the DSMB.
- Unlikely: The AE/SAE is doubtfully related to the investigational product or procedure.
- Unrelated: The AE/SAE is clearly NOT related to the investigational product or procedure.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator make an assessment of causality.

7.4.4 Expectedness

The following adverse events are considered to be expected as a result of the catheterization and infusion procedure:

- Disease-related adverse events are expected
- Some premature ventricular contractions, non-sustained ventricular tachycardia (<30 sec duration)
- Hypotension (Systolic Blood Pressure <80 mmHg) and/or bradycardia (Heart Rate <50 beats/min) that responds rapidly to fluid, atropine and possibly vasopressor administration, if required
- Reduction of coronary blood flow, TIMI flow grade I or II, persisting <3 min after balloon deflation, during cell infusion
- Angina, duration <10 min during cell infusion
- ST elevations, duration <3 min during cell infusion, troponin elevations above the 99th percentile but not more than 3x, at any time during the first 24 hours after cell infusion
- Coronary artery dissection
- Other risks of the infusion procedure include those risks that are possible with the study procedure. These include risks related to infection, bleeding, hypotension, pain and hematoma at the arterial puncture site, arrhythmia, sensitivity or allergy to radiographic contrast, exposure to radiation, thromboembolism, contrast induced nephropathy, myocardial ischemia or infarction.
- Bleeding, bruising and/or hematoma formation at the site of vascular access for the cell infusion procedure, at any time within the first 24 hours after cell infusion

All adverse events expected or otherwise, should be reported in the subject data. Serious Adverse

Events (SAEs) should be reported to the Sponsor within 24 hours of the site learning of the event.

7.4.5 Clinical Significance

An abnormal lab value or test result should be deemed clinically significant if either of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity that is new or has worsened from baseline.
- The abnormality is of a degree that requires additional active management, e.g., change of dose, discontinuation of a drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

A qualified physician at the investigative site, either the Investigator or a Sub-Investigator, will review all study-related laboratory and other test results. The reviewing Investigator will use his/her medical judgment to classify and document any results that are outside of the normal results range. The Investigator will indicate whether each abnormal result is clinically significant (CS) or not clinically significant (NCS) on the source document and case report form.

Once the Investigator deems an abnormal value to be clinically significant (CS), he or she will determine whether there is a clinical exam finding or symptom (new or pre-existing) that explains the abnormal value. A progress note summarizing the findings, including the reason(s) why the results are deemed CS will be written to provide documentation for an adverse event report. If the Investigator is able to provide a differential diagnosis for the CS result, he or she should describe the AE accordingly, e.g., urinary tract infection or suspected anemia. In the absence of an associated clinical sign or symptom, and if only a single value is deemed CS, list the abnormal value itself as the AE, e.g., elevated potassium or decreased calcium. As more information about the abnormal value is known that provides a diagnosis, the AE should be updated in the electronic data system to reflect the diagnosis.

7.4.6 Clinical Laboratory Adverse Events

Abnormal laboratory findings (e.g. clinical chemistry, hematology, and urinalysis) that are judged by the Investigator as clinically significant (CS) will be documented as described in Section 7.4.5 and will be recorded as AEs or SAEs if they meet the definition of an AE as defined in Section 7.4 or SAE, as defined in Section 7.4.7.1.

Clinically significant abnormal laboratory findings that are detected during the study or are present at screening and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study but do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant.

7.4.7 Serious Adverse Events

7.4.7.1 Definition

An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.
An adverse event or suspected adverse reaction is considered "**serious**" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Within the reporting requirement under 21 CFR 312.32(c)(1)(i), the meaning of *reasonable possibility* is defined by providing the following examples of types of evidence that would suggest a causal relationship between the drug and the adverse event.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for

elective treatment of a pre-existing condition that did not worsen from baseline is not considered to be an AE.

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (i.e., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

7.4.7.2 Reporting Serious Adverse Events

All SAEs, including any fatal or life-threatening event, must be reported within 24 hours from the time the Investigator is made aware of the event. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before recording the event in the data system and completing as much information known at the time of the submission. The reporting timeframes for any SAE occurring during the study are summarized in Table 3.

All SAEs are to be reported as follows:

- Site completes the SAE Report Form (initial and/or follow-up) and faxes the completed form to UBC Safety at 1-877-200-2945.

- UBC Safety will review all information provided and contact the Investigator for additional information, as necessary. The DSMB will receive regular safety updates from the Sponsor. The Sponsor or designee is responsible for notifying the DSMB of all SAEs as described in Table 3.

- Per ICH E2A and 21 CFR 312, regulatory agencies will be notified by the Sponsor by telephone or fax of any unexpected, SAR potentially associated with treatment as soon as possible, but in no event later than 15 calendar days after the Sponsor's initial receipt of the information; fatal or life-threatening unexpected SAEs associated with treatment will be reported to regulators within 7 calendar days. Follow-up information will be provided as required.

Table 3. Serious Adverse Event Reporting Requirements

Serious Adverse Event Reporting Requirements			
	Initial Reports		**Follow-Up Reports**
Type of SAE	Serious, Unexpected, Reasonable Possibility Causality	All Other SAEs	Any SAE
Reporting Timeframes (Site to Sponsor)	24 hours	24 hours	72 hours
Reporting Timeframes (Sponsor to DSMB)	Notification will occur in parallel with applicable Regulatory Agencies	Aggregate reporting at time of DSMB meetings	

All AEs and SAEs documented at a previous visit/contact that are designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs (including SAEs) will be followed until resolution, until no further changes in the event are expected (i.e. the point at which a subject experiencing an adverse event is treated successfully and stabilized even though they may continue to experience sequelae) as confirmed by the Investigator, until the subject is lost to follow-up, or until the subject's 12 Month Visit. Subjects will be contacted by phone annually through year 5 post-infusion to assess for MACE as described in Protocol Section 7.3.7. If a subject dies during participation in the study or during a recognized follow-up period, the Medical Monitor will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded by modifying the AE forms in the electronic data system.

The Investigator will promptly report all SAEs within the timeframes specified in Table 3. The Investigator will comply with the applicable local regulatory requirements related to reporting of SAEs to his or her Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

This protocol is being filed under an investigational study with the appropriate regulatory agencies. A given SAR may qualify for an Expedited Safety Report (ESR) if the SAE is serious, unexpected, and has a reasonable possibility that the drug caused the event. In this case, all Investigators participating in the study will receive the ESR. The purpose of the ESR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the product under investigation.

7.4.7.3 Sponsor Monitoring of Adverse Events

This study will be overseen by two distinct data safety monitoring boards (DSMBs): The National Heart, Lung and Blood Institute (NHLBI) DSMB will review the 14 subjects in the Safety Cohort and an independent DSMB appointed by the Sponsor will review the Randomized Cohort and will have access to all Safety Cohort reports and NHLBI DSMB recommendations.

The following list summarizes the Sponsor's role in monitoring AE/SAEs:

- All SAEs will be reviewed on a monthly basis by the Sponsor's Medical Monitor or designee.
- The Sponsor is responsible for notifying the DSMBs of all SAEs, and of any concerns regarding the frequency or type of SAE(s) on a study or treatment cohort.
- The Sponsor will prepare summary reports of all AEs/SAEs approximately every 6 months for the NHLBI-sponsored DSMB (Safety Cohort subjects) and for the study-sponsored DSMB (all subjects enrolled).

7.4.7.4 DSMB Monitoring of Adverse Events

This section generally applies to both the NHLBI and independent DSMB, but the NHLBI DSMB will review materials from only the fourteen subjects enrolled in the Safety Cohort. The following list summarizes roles of the DSMBs in monitoring AE/SAEs

- The DSMBs will review all SAEs. The Sponsor will report serious, unexpected and potentially related SAEs to the DSMB in parallel with reporting to applicable Regulatory Agencies. The DSMB chair (or designee) will be requested to acknowledge receipt of SAEs within 72 hours of notification.
- Approximately every six months the DSMBs will be provided with a summary (aggregate) of all AEs and SAEs, regardless of attribution, and additional safety and outcomes data as part of their scheduled interim reviews. In addition to AE and SAE review, specific safety and outcomes data will be identified for review by the DSMBs.
- The DSMB Chair (or designee, e.g., NHLBI Project Officer) is responsible for reviewing the SAE materials to determine if the documents are complete. If there are any concerns regarding the type or frequency of the event, the DSMB Chair may request additional information from the Sponsor. The DSMB Chair will determine whether additional DSMB review is required and make recommendations to the Sponsor regarding continuation of the study.

7.4.8 Post-Study Adverse Events and Serious Adverse Events

The Investigator should notify the Medical Monitor of any death or SAE occurring at any time after a subject has completed or terminated a clinical trial, when such death or SAE may reasonably be related to the study therapy used in this investigational trial. Investigators are not obligated to actively seek AEs from former study participants.

7.5 Removal of Subjects from the Trial or Study Drug

The Investigator may withdraw a subject from participation in the study for any of the following

reasons:

- A protocol violation occurs,
- An intolerable adverse event occurs, that affects continuation of subject's participation in the study,
- The Sponsor or Investigator terminates the study, or
- The subject requests to be discontinued from the study.

Subjects who become pregnant during the study following the study infusion will be followed during the pregnancy and through birth of the newborn. Subjects who become pregnant prior to receiving the study infusion will be withdrawn from the study.

7.6 Other Study Procedures

For subjects who so consent, serum for clinical research into biomarkers will be collected at every scheduled visit and sent to the Sponsor for analysis.

7.7 Appropriateness of Measurements

Usual safety measurements will be obtained and summarized per standard reporting. In addition, more in depth evaluation of safety data as it relates to cardiac events will more fully elucidate the safety profile for CAP-1002. Events to be assessed in greater detail include all MACE events, myocarditis, change in TIMI flow to ≤1 following infusion, troponin and CK- MB elevations, ventricular tachycardia events, and increases in anti-HLA antibodies as indicative of sensitization to CAP-1002 donor antigens.

With respect to efficacy, the perfect surrogate remains elusive in terms of cardiac disease given the complexity of the heart failure syndrome. Data suggest that markers of the biological process of left ventricular hypertrophy and enlargement (remodeling) and the factors that contribute to this process may be viewed as surrogates for progression of the disease as may functional measures and neurohormones (Anand, Florea, & Fisher, 2002). More specifically, it has been shown that the validity for infarct size as measured by MRI under a common imaging protocol is relatively high when used as a surrogate endpoint for clinical outcomes (Desch et al., 2011). In addition, the ability of infarct size to predict clinical endpoints has been demonstrated in epidemiological studies (Larose et al., 2010; Wu et al., 2008).

In this trial, the primary efficacy endpoint is change in infarct size (relative to LV size). Infarct size represents the extent of myocardial injury sustained after an MI. Infarct size is likely the single most important defining factor of the remodeling process, leading to change in function, volume and geometry of the LV. Use of a common imaging protocol in the study ensures high measurement reliability for infarct size. Infarct size may prove in this study, as in prior studies, to be a reasonable MRI surrogate endpoint that correlates with long term subject outcome.

7.8 Payment to Subjects

Subjects will be paid $100, as applicable in clinical site budgets, for the Screening, Infusion, Month 6, and Month 12 visits. Subjects will be paid $50 for all other visits (Week 2, and Months

1, 2 and 3). These disbursements are intended to cover the costs required to complete these study visits. Necessary travel expenses (reasonable hotel, meals and fuel) and parking expenses may be reimbursed, depending on the individual circumstances. Study staff will contact the Sponsor to request reimbursement on a case by case basis.

The total amount the subject will receive if they complete the whole study is $550. Safety Cohort subjects will receive up to $650 for extra testing and visits conducted in the Phase I portion of the study. Subjects will only be paid for those visits and procedures that they complete.

7.9 Early Termination Procedures

Every reasonable effort will be made to retain subjects in the study. In the event that a subject must be withdrawn from the study early, study personnel should attempt to obtain testing and data required for the 12 Month Visit (see Section 7.3.6) as well as the reason for withdrawal, if known. If the subject permits, he or she should be contacted by study personnel at the time of their usual study visits (and annually through 5 years post-infusion), as described in the protocol.

Follow-up of adverse events that result in discontinuing the subject from the study will continue until resolution, until the event has stabilized as confirmed by the Investigator, or until the event has been determined to be caused by an agent other than the study drug.

All consenting subjects, including those who discontinued early from the study, will be contacted by phone annually on the anniversary of their infusion through year 5 post-infusion to assess for MACE, defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant.

A subject can be considered “lost to follow-up” if he or she misses a visit and study personnel are unable to contact him or her in a timely manner with a minimum of three documented phone calls. If contact with the subject is not accomplished, study personnel should follow-up with certified mail in the following manner:

1. Mail a certified letter with return receipt requesting contact and expressing concern for the subject’s well-being.
2. If the subject does not respond within seven days, mail another certified letter with return receipt stating that the subject’s participation in the study has been terminated.
3. If a signed mailing receipt for the second letter is returned, record the termination date as the date the subject signed it. Otherwise, record the termination date as the date the second letter was mailed.

8 QUALITY CONTROL AND ASSURANCE

Data will be entered using an EDC system. A detailed description of the data collection tools and data management process can be found in the case report form completion guidelines and other data management materials that will be provided to each site. The site must ensure appropriate source data documentation. The Investigator or designee must enter all required subject data in the EDC system in a timely fashion (within 3 weeks of study visit) and an explanation must be documented for any missing data.

A site initiation visit will be conducted at each site participating in the Safety and Randomized Cohorts prior to subject enrollment. During this visit, there will be a review of the study protocol, study procedures, the case report forms, the data collection and submission process, and the site's regulatory obligations as well as any special procedures with the center personnel. A representative from the Sponsor will lead the site initiation visits. All training will be documented. A formal, centralized investigator meeting will be held prior to initiation of enrollment for the Randomized Cohort accompanied by site initiation visits if required/desired by site or Sponsor.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

The Statistical Analysis Plan (SAP) for the Phase 1 Safety Cohort was drafted prior to the start of Phase 1 enrollment with modifications made in the analysis over time based on requests from DSMB during Phase 1.

Pre-specified analyses will be detailed in a Statistical Analysis Plan (SAP). Descriptive summaries will be provided for all safety and efficacy parameters by cohort (Primary or Exploratory) and stratum (recent or chronic MI). Primary efficacy analyses will be performed for the analysis population using a modified intent-to-treat population with post-baseline outcome data. Handling of missing data will be addressed in the SAP.

All analyses and reports will be developed and validated per Good Clinical Practices. An independent DSMB will monitor the study and make recommendations, if needed, regarding stopping the study due to safety concerns.

9.2 Determination of Sample Size

In total, a maximum of approximately one hundred thirty-four (134) subjects with a MI and resulting ischemic left ventricular dysfunction meeting all inclusion and no exclusion criteria will be enrolled. The first fourteen (14) subjects (7 Recent MI and 7 Chronic MI) will receive CAP-1002 open-label and will be designated as the Safety Cohort. The approximate maximums of one hundred three (103) subjects in the Primary Randomized Cohort (51-52 Recent MI and 51-52 Chronic MI) and the up to 17 subjects in the Exploratory Randomized Cohort will begin to enroll only after DSMB review of the Safety Cohort data and recommendation to proceed. These approximately 120 subjects in the Primary Randomized Cohort and Exploratory Randomized Cohort will be independently randomized in a double-blind fashion to receive either CAP-1002 or placebo in a 2:1 ratio, favoring CAP-1002 to achieve approximately up to 93 subjects with complete 12 month data in the Randomized Cohort. A balancing algorithm will be used to ensure site-specific balancing to the 2:1 allocation after stratifying for prior MI.

The Safety Cohort was evaluated once all subjects reached the primary safety endpoint assessed at the 1 month visit. With n=14, if no significant safety events are observed, the one-sided 95% upper bound for the true rate of significant events would be < 20%. The DSMB conducted a review of the Safety Cohort data and made a recommendation to proceed with randomization of the next 120 subjects. Efficacy and safety will be assessed at all post-screening visits, although

MRI testing will only be completed at 6 and 12 months; the 12 month visit is the primary efficacy endpoint.

Historical Data

The CADUCEUS and ALLSTAR Safety Cohort data provide some background for planning sample size to test for efficacy. The efficacy endpoints in the CADUCEUS study and in the ALLSTAR Safety Cohort included the relative change in the Month 6 and 12 outcomes relative to baseline as judged by MRI assessment of infarct size (measured in %). Assumptions used for power calculations are summarized below in Table 4 with the relative change displayed as a percent improvement from baseline. The ALLSTAR Safety Cohort was used for the assumed means and SDs and CADUCEUS was used for the treatment effect in Chronic MI patients relative to Recent MI.

Table 4. Sample Size Assumptions

	Month 6		Month 12	
	Mean	SD	Mean	SD
CAP-1002 Recent	6.20	10.00	14.70	10.00
CAP-1002 Chronic	3.10	10.00	7.35	10.00
Placebo	0.00	10.00	0.00	10.00

Power calculations using Monte Carlo simulation indicated that, under these assumptions, the trial will have more than 90% power to be declared successful with a total sample size of 100.

Primary Randomized Cohort

The Primary Randomized Cohort is designed to assess the efficacy of the study agent as well as further evaluate the safety profile of CAP-1002. Up to 103 subjects will be enrolled in the Primary Randomized Cohort. This maximum sample size is based on the Recent and Chronic MI strata being analyzed independently with a treatment effect of 15% at Month 12 for each strata, a pooled standard deviation of 10%, a minimum power of 80%, and a significance level (alpha) of 0.05.

Exploratory Randomized Cohort

The Exploratory Randomized Cohort sample size of up to 17 subjects was estimated based on DSA results observed in the Safety Cohort, where approximately 14% of the screened subjects had pre-formed antibodies to all available donors. That is, assuming a 14% rate of pre-formed DSAs, approximately 120 subjects would be screened to achieve enrollment of 103 in the matched Primary Randomized Cohort, thus yielding up to 17 subjects enrolled in the Exploratory Randomized Cohort. Enrollment into the Exploratory Randomized Cohort is capped at n=17, with no pre-specified limit for subject counts in the Recent and Chronic stratum. Enrollment in the study will be complete when the Primary Randomized Cohort is fully enrolled, regardless of whether the Exploratory Randomized Cohort has enrolled.

9.3 Analysis Populations

Treated subjects (those who have undergone infusion) from all Cohorts will be followed for 12

months. Subjects will have study visits at 2 weeks, 1, 3, 6, and 12 months following infusion. Subjects enrolled in the Safety Cohort will also have a 2 month study visit.

The analysis population for assessing safety will consist of all subjects in a given Cohort (Safety, Randomized) who received an infusion of either CAP-1002 or placebo. The primary analysis population for assessing efficacy will consist of all subjects in the safety population from Primary Randomized Cohort (Primary Modified Intent-to-Treat (mITT) Population) who had a baseline observation and at least one post-baseline observation. The Safety Cohort subjects will be summarized and analyzed distinctly from the Randomized Cohort due to the unblinded nature of the treatment assignment. Similarly, the Exploratory Randomized Cohort of mismatched subjects will also be summarized distinctly from the Primary Randomized Cohort. Details on additional analysis populations will be addressed in the SAP.

9.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics of all accrued subjects such as race, ethnicity, sex, and age will be summarized and reported. The gender and minority distributions are expected to reflect a highly multicultural infarct subject population. There are no particular recruitment strategies for women or minorities.

9.5 Primary Endpoint(s)

9.5.1 Primary Safety Endpoint(s)

Medical Dictionary for Regulatory Activities (MedDRA) will be used for this study to code adverse events.

The primary safety endpoint is the proportion of subjects experiencing any of the following adjudicated events within one month following intracoronary infusion:

1. Acute myocarditis possibly attributable to CAP-1002 or placebo, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002 or placebo, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo.
2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting, or during routine ECG monitoring while hospitalized.
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
4. Major adverse cardiac event (MACE), defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or CK-MB levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be

accompanied by symptoms of ischemia >20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality.

Point estimates and two-sided 95% confidence intervals for the proportion of subjects who experience any of the four events will be presented. Similarly, each of the four endpoints will be summarized separately with point estimates and two-sided 95% confidence intervals for the proportion of subjects who experience each event within the first month post-infusion. Also, two-sided 95% confidence intervals will be constructed for the difference between CAP-1002 and placebo and a two-sided Fisher Exact test will be used to compare the treatments for the Safety Analysis Set.

9.5.2 Primary Efficacy

The primary efficacy objective is to determine if the administration of CAP-1002 by intracoronary infusion may result in structural cardiac benefits for subjects with ischemic left ventricular dysfunction and a previous MI as measured by the percent change from baseline in the MRI assessment of infarct size as a percent of left ventricular mass at 12 months post administration. Baseline assessments are conducted during the "Screening" visit, prior to the administration of CAP-1002 or placebo.

The primary efficacy hypothesis is that CAP-1002 is superior to placebo in reducing infarct size in either all subjects combined ("full group") or in subjects with recent MI ("subgroup"). A closed testing procedure will be used so that strong control of type 1 error is maintained. Specifically, the following hypothesis sets will be tested:

1) H_{o_s}: $\mu_{c\_s} - \mu_{p\_s} = 0$ or H_{o_f}: $\mu_{c\_f} - \mu_{p\_f} = 0$
   H_{a_s}: $\mu_{c\_s} - \mu_{p\_s} < 0$ H_{a_f}: $\mu_{c\_f} - \mu_{p\_f} < 0$

   and

2) $H_{o\_s} \cap H_{o\_f}$: $\mu_{c\_s} - \mu_{p\_s} = 0$ and $\mu_{c\_f} - \mu_{p\_f} = 0$
   $H_{a\_s} \cap H_{a\_f}$: $\mu_{c\_s} - \mu_{p\_s} < 0$ or $\mu_{c\_f} - \mu_{p\_f} < 0$

where *s* denotes the subgroup, *f* denotes the full group, μ_{c_s} and μ_{p_s} are mean percent changes in the CAP-1002 and placebo treatment groups, respectively, in the subgroup, and μ_{c_f} and μ_{p_f} are mean percent changes in the CAP-1002 and placebo treatment groups, respectively, in the full group.

Therefore, both the intersection null hypothesis ($H_{o\_s} \cap H_{o\_f}$) and either of the individual null hypotheses (H_{o_s} or H_{o_f}) must be rejected at the (one-sided) 0.025 significance level for the trial to be declared a success. In other words, the null hypothesis of "no treatment effect in the full group and no treatment effect in the recent MI subgroup" must be rejected at the one-side 0.025 significance level, necessarily meaning that either the result is significant in the full group, in the recent MI subgroup, or both. The results of the tests of the individual hypotheses (also at the one-sided 0.025 significance level) determines which specific comparisons are significant.

The primary analysis will be a longitudinal mixed effects model. The response variable of percent change from baseline in infarct size as a percent of left ventricular mass will be modeled with the fixed categorical effects of treatment group and time (6 and 12 months), as well as a continuous fixed covariate of baseline infarct size. Intercept and subjects will be treated as random in this mixed effects model. The primary hypothesis will be tested using the estimate of treatment effect compared to placebo at 12 months. An additional test will compare the treatments at 6 months and will be considered secondary. Model results will be provided for fixed affects and estimates for each level of each affect. A mean profile plot will be presented to describe the treatment response over time.

The final primary efficacy analysis population will depend on the results of the adaptive design interim analysis. The final analysis will use the above model and the study result will depend on the result of a Dunnett intersection test p-value calculated from the final mixed model results similarly to the interim. The adaptive design interim analysis conducted on approximately 80 subjects with 6 month follow-up data in the Primary Randomized Cohort across the Recent MI and Chronic MI strata will determine whether the analysis will be based on the strata combined or the Recent MI strata alone. See the Adaptive Design IAP for details.

9.6 Secondary Endpoint(s)

9.6.1 Secondary Safety Endpoint(s)

The following adjudicated events will be evaluated as secondary safety endpoints during the twelve-month follow-up period:

1. Acute myocarditis possibly attributable to CAP-1002 or placebo, diagnosed with consideration of clinical context, with or without a clinically indicated endomyocardial biopsy. In order to be considered related to CAP-1002 or placebo, humoral or cellular immune reaction specific to CAP-1002 must also be documented for subjects treated with CAP-1002, or a temporal relationship with IP administration must exist for subjects administered placebo.
2. Death due to ventricular tachycardia or ventricular fibrillation defined as occurring with prior ECG documentation of these arrhythmias during ambulatory ECG monitoring in an outpatient setting or during routine ECG monitoring while hospitalized.
3. Sudden unexpected death defined as occurring within one hour of symptom onset, or un-witnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.
4. Major adverse cardiac event (MACE), defined as the composite incidence of death, non- fatal recurrent MI, hospitalization for heart failure, emergency room treatment for heart failure (NT-proBNP >450 pg/mL or BNP>100 pg/ml, with treatment including intravenous diuretic administration), left ventricular assist device (LVAD) placement or heart transplant. Peri-infusion MI will be defined as presence of troponin or CK-MB levels > 5 times the upper reference limit during the 24 hours following infusion. These elevations must be accompanied by symptoms of ischemia > 20 minutes in duration and ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium, or

new regional wall motion abnormality.
5. New cardiac tumor formation on MRI imaging.
6. Any hospitalization due to a cardiovascular cause or related to CAP-1002 or placebo infusion.
7. Any inter-current cardiovascular illness or one related to CAP-1002 or placebo infusion, which prolongs hospitalization. Evidence of myocardial injury will be assessed by a rule out MI cardiac enzyme protocol performed following administration of CAP-1002 or placebo. Troponin and CK-MB will be obtained approximately every 8 hours for the first 24 hours after infusion.
8. New TIMI flow ≤1, following intracoronary infusion of CAP-1002 or placebo.
9. Development of, or an increase in the frequency of, ventricular tachycardia with a duration of 30 beats or longer ascertained by periodic, protocol-mandated 24 hour ambulatory ECG monitoring.
10. Development of increased anti-HLA antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor.

9.6.2 Secondary Efficacy

All comparisons in the secondary analyses will be based on a null hypothesis of no difference in the endpoint between subjects administered CAP-1002 as compared to placebo and an alternate hypothesis of a difference in the endpoint for subjects administered CAP-1002 as compared to placebo. Secondary analyses will be based on a random effects model similar to the primary but will be based on an alpha of 0.05 without controlling for multiplicity.

The following secondary efficacy endpoints will be evaluated during the six-month and twelve-month follow-up periods:

Global LV Function measures

1. Percent change and change from baseline in MRI assessment of LVEF
2. Percent change and change from baseline in MRI assessment of left ventricular end-diastolic and end-systolic volumes indexed to BSA

Structural measures

3. Change from baseline in MRI assessment of infarct size as a percent of left ventricular mass
4. Percent change and change from baseline in MRI assessment of infarct size expressed in grams
5. Percent change and change from baseline in MRI assessment of viable mass expressed in grams

Regional measure

6. Percent change and change from baseline in MRI assessment of function in the region which received CAP-1002 therapy

Clinical function/status measures

7. Changes from baseline in distance covered in six minute walk test

8. Change from baseline in Minnesota Living with Heart Failure Questionnaire (MLHFQ) score
9. Change from baseline in SF-36 score
10. Change from baseline in WPAI:SPH score
11. Change from baseline in Patient Global Assessment (PGA) score
12. Change from baseline in NYHA Class

Biomarker

13. Percent change and change from baseline in NT-proBNP
14. Change from baseline in log transformed NT-proBNP

Additional detail regarding secondary endpoint analyses can be found in the SAP.

Analyses of the secondary efficacy endpoints will be performed using the same longitudinal modeling approach as the primary efficacy endpoint; the baseline covariate used in the model will be the baseline of the endpoint being analyzed. Two-sided testing will be performed at level p=0.05.

A correlational analysis will be presented (for tissue based and functional measures) with Pearson's correlation coefficient for all possible pairs of efficacy endpoints and where appropriate the Spearman's correlation coefficient will be presented.

9.7 Administrative Interim Analysis

An interim safety and efficacy analysis will be performed after all Primary Randomized Cohort subjects have completed 6 months of follow-up. This is a pre-planned final analysis of the final 6 month data. This analysis will be unblinded. The analysis results will be used for planning of Phase III activities and will have no effect on the conduct of the study. This interim analysis will be considered administrative and no adjustments to the study alpha will be made.

Subjects, investigators, and Sponsor's personnel who had direct responsibility for monitoring at the sites will be blinded throughout the study. Following the interim analyses planned for the determination of efficacy at 6 months, the appropriate Sponsor representatives will be unblinded in order to review and make decisions regarding entry into Phase III clinical development. Sponsor personnel will be unblinded to pooled, group data but not to individual, subject level data. Personnel with access to the unblinded data and analysis results will be detailed in an unblinding memorandum to be filed in the Trial Master File. Unblinded interim data and analysis results will be kept confidential from other company personnel involved with trial conduct and from investigators, patients, and their families.

9.8 Study Stopping Guidelines

9.8.1 Safety Cohort (Phase I)

This guideline is to be used to indicate boundaries requiring discussion by the DSMB and is designed to assist the independent NHLBI-appointed DSMB in overseeing the study. The DSMB may also request additional interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of subjects in the study. Monitoring of primary safety endpoints will be conducted. All SAEs will be reported to the DSMB for review.

The proportion of subjects experiencing serious procedure-related outcomes (SPROs) will be monitored using a stopping guideline to be consistent with an external standard for safety in subjects undergoing angioplasty and stent placement. A 20% patient-specific probability (PSP) among CAP-1002 -treated subjects would be the upper bound of acceptability. The study may be stopped if two subjects experience a SPRO.

9.8.2 Randomized Cohort (Phase II)

Safety will continue to be assessed by the DSMB by comparing the PSP between the randomized CAP-1002 and placebo groups. The Sponsor will engage an independent DSMB to monitor the boundaries requiring discussion in overseeing the study. The DSMB may also request additional interim analyses and develop other criteria for determining when to intervene in the enrollment or treatment of subjects in the study. Monitoring of all safety endpoints will be conducted. Individual cases reported to regulatory bodies will also be reported to the DSMB Chair and will be reviewed by the DSMB at each meeting. The DSMB will also have access to all reports pertaining to the comparison of CAP-1002 to placebo, including any related literature of external concerns.

The proportion of subjects experiencing SPROs will be monitored at pre-planned intervals set by the DSMB. A series of charts (n=60, 120, 180, and 234) have been created to assist with this oversight (see Appendix 3); the thresholds for ruling out a 10% absolute excess decreases as data accrue. These charts were computed using a one-sided 95% Fisher Exact test over a broad range of possible SPRO outcomes. No Type I error adjustment will be made for repeated safety looks since the ultimate decision regarding safety represents a clinical decision involving all safety endpoints as an additional obligation beyond efficacy. The DSMB will also monitor efficacy but no futility analyses for efficacy are planned.

9.8.3 Exploratory Randomized Cohort (Phase II)

There are no formal stopping guidelines for this group. In general, these subjects will be considered independently of the Primary Randomized Cohort, but will be reviewed in detail by the DSMB as are all other subjects. Any safety concerns will be considered by the DSMB in the context of the greater study, including the Primary Randomized Cohort. Should safety concerns arise in the Exploratory Randomized Cohort, the DSMB will make a recommendation regarding continuing of enrollment of mismatched subjects into the study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

A complete list of participating Investigators and institutions will be maintained by the Sponsor and will be posted at http:/www.clinicaltrials.gov in the listing for this study.
Should a question arise during the study from the Investigator or study staff, the staff may contact the ALLSTAR Sponsor staff using the current study contact information as provided on http:/www.clinicaltrials.gov in the listing for this study.:

Contact information for the Medical Monitor for the study is provided below:

Sponsor Medical Monitor:
[redacted]

Study Monitors (Clinical Research Associates) will also be assigned to this study and contact information will be provided to the sites throughout the study.

The lead Principal Investigators are [redacted]

[redacted] were responsible for enrolling subjects in the Safety Cohort of subjects. Approximately 45 sites will support enrollment.

Contract research organizations (CROs) will be used, at the Sponsor's direction, for site monitoring, data management, and some analyses and reporting for the study. A core imaging group will be used to centrally read all MRIs and a core laboratory will be used to analyze samples for HLA typing, DSA monitoring and cellular immune response (ELISpot). Contact information for these groups will be provided to the sites prior to the start of the study.

In order to ensure quality and continuance of patient care, it is highly recommended that the subject inform his/her primary cardiac care physician of his/her participation in ALLSTAR.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

It is the Investigators' responsibility to ensure that, prior to initiating this study, this protocol is reviewed and approved by the appropriate local Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The composition and conduct of this committee must conform to the United States CFR and ICH E6.

The IRB/IEC must also review and approve the site's informed consent form (ICF), other written information provided to the subject and all advertisements that may be used for subject recruitment.

If it is necessary to amend the protocol or the ICF during the study, the Investigator will be responsible for ensuring that the IRB/IEC reviews and approves these amended documents. An IRB/IEC approval of the amended protocol and/or ICF must be obtained in writing before implementation of the amended procedures and before new subjects are consented to participate in the study using the amended version of the ICF.

10.3 Ethical Conduct of the Study

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

10.4 Subject Information and Consent

Before being admitted to the clinical study, all subjects must consent in writing to participate. An ICF will be given to each subject, which will contain all United States federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act (HIPAA) authorization information in language that is understandable to the subject.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator will review the study with each subject. The review will include the nature, scope, procedures, and possible consequences of the subject's participation in the study. The ICF and review will be in a form understandable to the subject. The Investigator or designee and the subject must both sign and date the ICF after review and before the subject can participate in the study. The subject will receive a copy of the signed and dated form, and the original will be retained in the site study files. The Investigator or his/her designee will emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB/IEC. The site must use the amended consent form for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

10.5 Subject Confidentiality

Subjects' names will remain confidential; only subject number and birth date will be recorded in the database. If the subject name appears on any other document collected (e.g., hospital discharge summary), the name will be obliterated before the document is transmitted. All study findings will be stored in electronic databases. The subjects will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IRB/IEC to inspect their medical records to verify the information collected.

Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA.

All participants in the study will provide written authorization to disclose private health information either as a part of the written ICF or as a separate authorization form. The authorization will contain all required elements specified by 45 CFR 164 and ICH E6 as applicable, and will contain a waiver of subject access to study-related private health information until the conclusion of the clinical study. The authorization will remain valid and in full force and effect until the first to occur of (1) the expiration of 2 years after the study therapy is approved for the indication being studied, or (2) the expiration of 2 years after the research program is discontinued. Individual subject medical information obtained during this study is confidential and its disclosure to third parties (other than those mentioned in this section) is strictly prohibited. In addition, medical information obtained during this study may be provided to the subject's personal physician or to other appropriate medical personnel when required in connection with the subject's continued health and welfare.

The Sponsor will maintain a personal subject identification list (subject and treatment numbers with the corresponding subject names) to enable records to be identified.

10.6 Study Monitoring

The Sponsor will provide study monitors and will determine the frequency of monitoring visits primarily based on individual site enrollment and site compliance with protocol- dictated procedures, with visits generally occurring once every 2-4 months. All sites will be monitored shortly after the first subject at the site completes the Infusion Visit. Additionally, study monitors will have continuous access to the electronic data capture (EDC) system to review completion of study documents, data and adverse event reporting in a timely manner.

10.7 Case Report Forms and Study Records

All CRFs will be completed in accordance with GCP guidelines and as soon as possible after each clinical trial visit.

An electronic data capture (EDC) system will be utilized to record all of the protocol required information to be reported to the Sponsor on each trial subject. In the event that the EDC system is not functioning or accessible, a paper case report form (CRF) will be utilized in the interim and later entered into the EDC system. Study personnel from each site will be trained in how to access and use the EDC system to enter and transmit data for the study. Study personnel will be given a "sign in" and password unique to them which will not be used by any other personnel. Study personnel will be trained regarding proper correction of data entries in the EDC system.

Study personnel are responsible to ensure that all entries are accurate, legible and verifiable with the source data in the medical record. A source document is defined as the place in the medical record where a given data point first appears. CRFs will not serve as source documents.

10.8 Data Monitoring Committee

Safety Cohort

The NHLBI Data and Safety Monitoring Board (DSMB) will oversee subjects enrolled in the Safety Cohort. Interim data reviews will be conducted at times coincident with regularly scheduled meetings of the NHLBI-appointed DSMB in accordance with reaching accrual and follow up milestones. The DSMB Chair will be notified each time that an SAE occurs. The DSMB evaluated unblinded AE data (including SAEs) in the Safety Cohort after the initial 4 subjects were treated with 12.5 M CDCs, after the first 4 subjects were treated with 25M CDCs and again when all 14 subjects completed their one month study visit (the primary endpoint) to trigger the initiation of the Randomized Cohort. The NHLBI DSMB also reviewed the Safety Cohort after all 14 subjects competed their 2 month and their 6 month follow up visits. They reviewed enzyme evidence of any infarction within 24 hours of the infusion and any evidence of arrhythmias during the month following infusion, as well as echocardiography, anti-HLA antibody immunoassay, ELISpot immunoassay and cardiac enzyme data collected at the one month study visit; this review occurred prior to proceeding with the Randomized Cohort. Other safety data, including the laboratory values were also evaluated by the DSMB as appropriate. Policies of the DSMB are described in the NHLBI DSMB Charter. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment. Stopping will be at the discretion of the Sponsor, after consideration of DSMB recommendation.

Randomized Cohort

An independent DSMB appointed by the Sponsor will oversee the Randomized Cohort and will observe the activities of the NHLBI DSMB during the Safety Cohort. The Randomized Cohort will begin only after the NHLBI DSMB has conducted a review of the 14 Safety Cohort subjects' one-month safety data. Interim data reviews during the Randomized Cohort will be conducted at times coincident with regularly scheduled meetings of the DSMB at intervals not to exceed 6 months apart. The DSMB will evaluate unblinded safety at all meetings; this will include all safety datain the form of tables, figures, listings, and narratives. The DSMB Chair

will be notified each time that an SAE occurs. They will review MRI data collected at the six month study visit. Other safety data, including the laboratory values will also be evaluated by the DSMB as appropriate. Monitoring of key safety endpoints will be conducted as described above, and if rates significantly exceed preset thresholds, the Sponsor will be notified and information will be supplied to the DSMB. Policies of the DSMB will be described in the DSMB Charter. The stopping guidelines serve as a trigger for consultation with the DSMB for additional review, and are not formal "stopping rules" that would mandate automatic closure of study enrollment. Stopping will be at the discretion of the Sponsor, after consideration of DSMB recommendation.

10.9 Protocol Violations/Deviations

As they occur, protocol violations (i.e., events that have potential to impact interpretation of data for intended population, such as violations of inclusion/exclusion criteria) and deviations (i.e., variations from protocol-specified processes unlikely to impact interpretation of data for intended population) will be documented at each site and reported to the Sponsor. Upon detection of a violation, the Sponsor will ensure reporting to the proper local and federal regulatory authorities in accordance with all applicable federal and local regulations. The Sponsor will determine the course of action based on the severity of the deviation or violation. These may include but are not limited to, withdrawal of the subject, additional training at the site, additional site monitoring, etc. In addition, the medical director and statistician will review the circumstances of each violation (in a blinded fashion) to determine whether the data can reasonably be included in the per protocol final analysis.

10.10 Access to Source Documentation

The Investigator, Sponsor's monitor and site clinical study personnel will be able to access the source documentation. De-identified source documentation may be accessed by the Sponsor and the DSMB, e.g., in evaluation of an SAE. In addition, the study site must allow trial-related monitoring audits, IRB/IEC review, and regulatory inspection(s), with direct access to source data and documents.

10.11 Data Generation and Analysis

Contract research organizations (CROs) will provide data management and analysis and reporting services to the Sponsor. A validated EDC system proprietary to the CRO will be utilized to collect data and generate a database. Study sites will be responsible for entering data collected at the site. External data sources (i.e., central labs and core imaging center) are expected either to provide data sets for electronic upload into the EDC database or enter the appropriate data directly into the EDC system. Data queries will be generated by the EDC system and by CRO data managers and then forwarded to the sites for resolution. As part of database quality assurance, critical fields (e.g., key efficacy and safety parameters) will be 100% verified between the database and e-CRFs and 10% of all other data pages will also be audited by the CRO.

10.12 Retention of Data

In accordance with 21 CFR 312.62, an Investigator participating in this study shall retain records, including the case report forms and supporting data including signed and dated consent forms, and medical records, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Records are required to be maintained for a period of 2 years following the date the marketing application is approved or, if no application is to be filed or if the application is not approved by the appropriate regulatory agencies, until 2 years after the investigation is discontinued and appropriate regulatory agencies are notified. In any case, the Sponsor should be notified prior to the destruction of any study records.

10.13 Financial Disclosure

In accordance with regulatory requirements, 21 CFR 54.4, the Clinical Investigators and Sub-Investigators at each site will be required to complete a financial disclosure form provided by the Sponsor prior to participation in the study. Each Clinical Investigator/Sub- Investigator shall provide to the Sponsor of the study sufficient accurate financial information to allow the Sponsor to submit complete and accurate certification or disclosure statements (Forms 3454 and/or 3455) as required by the appropriate regulatory agency regulations. Each Clinical Investigator/Sub-Investigator shall promptly update this information if any relevant changes occur in the course of the study or for 1 year following completion of the study.

10.14 Publication, Use and Disclosure Policy

Unless the Sponsor has given its written consent in advance or unless otherwise provided in the Clinical Trial Agreement executed by the parties with respect to the study, neither the Institution where the study is being conducted nor any Clinical Investigator/Sub-Investigator or study personnel may publish Sponsor confidential information or study data, disclose Sponsor confidential information or study data to any third party, or use Sponsor confidential information or study data for any purpose other than the performance of the study.

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Appendix 1 Schedule of Events[8]

Study Procedure	Screening	Pre-Infusion	Infusion	2 Weeks	1 Month	2 Months (Phase 1 Only)	3 Months	6 Months	12 Months /ET	24, 36, 48, 60 Months Follow-Up
Study Day	Day -28	Day 0	Day 0	Day 14 ±3d	Day 30 ±3d	Day 60 ±6d	Day 90 ±6d	Day 180 ±6d	Day 360 ±6d or ET	Annual ±2w
Relative Timing	Post-MI	≤28d Screen	≤28d Screen	Post Infusion	Post Infusion	Post Infusion	Post Infusion	Post Infusion	Post Infusion	Post Infusion
Informed Consent	X [1]									
Medical History	X [1]	X								
Limited Physical Examination	X [2]								X	
History and Cardiac Physical	X [2]	X	X	X	X	X	X	X	X	
Medication Review	X [1]	X	X	X	X	X	X	X	X	
Adverse Events Assessment	X [2]	X	X	X	X	X	X	X	X	
Major Adverse Cardiac Events			X	X	X	X	X	X	X	X
Vital Signs	X [2]	X	X	X	X	X	X	X	X	
12-Lead ECG	X [2]	X	X	X	X	X	X	X	X	
Hematology, Chemistry, & Urinalysis	X [1,2]	X	X	X	X	X	X	X	X	
PTT / INR		X [6]								
Serum NT-proBNP	X [2]	X	X	X	X	X	X	X	X	
Serum for Biomarkers	X [2,7]			X [7]	X [7]	X [7]	X [7]	X [7]	X	
Serum β-HCG	X [1,2,8]									
HIV & Hepatitis Screens; Hemoglobin A1c (HbA1c)	X [1]									
Donor Specific Antibody (DSA)	X [2,10]			X [10]	X [10]	X [10]	X [10]	X [10]	X	
HLA Typing	X [10]									
ELISpot	X [10]				X [10]					
Cardiac MRI	X [2]							X	X	
Chest, Abdomen, and Pelvis CT	X [2]									
24 Hour Ambulatory ECG	X [2]		X [11]		X	X		X	X	
Serum troponin & CK-MB		X [9]	X [9]	X	X					
Echocardiography	X [2]				X					
NYHA Functional Class	X [2]				X	X	X	X	X	
Six Minute Walk Test	X [2]							X	X	
Patient Questionnaires	X [2,12]							X [12]	X [12]	
Intracoronary Infusion; 24 Hr Hospitalization w/ Continuous			X							

[1] Permitted within 28 days immediately following index MI: signing ICF, review of medical history, review of concomitant medications, and collection of laboratory samples required for assessment of study eligibility criteria (e.g., eGFR, HbA1c, hepatitis serology, HIV serology, LFTs, hematocrit, WBC, serum β-HCG and platelet count).

[2] Must be performed >28 days post-MI and ≤28 days of infusion. Repeat hematology, chemistry & urinalysis if initial testing to assess eligibility falls outside of this window. For post infusion, urinalysis only.

[3] Every 8 hours from time of infusion until discharge.

[4] On day of discharge.

[5] Urinalysis only.

[6] For subjects on anticoagulation therapy only.

[7] Only if additional consent is obtained; collection for shipment to central laboratory.

[8] Non-postmenopausal females only.

[9] Troponin and CK-MB pre-infusion and approximately every 8 hours post infusion.

[10] Collection of blood for testing at central laboratory.

[11] Starting immediately prior to discharge for 24 hours.

[12] MLHFQ, SF-36, WPAI:SHP and Patient Global Assessment.

Appendix 2 Prohibited Concomitant Medications

The following medications are prohibited for three months prior to enrollment in the study:

GENERIC NAME	TRADE NAME
Abacavir	Epzicom®
Abacavir	Ziagen®
Abacavir sulfate, Lamivudine, and Zidovudine	Trizivir®
Adalimumab	Humira®
Aldesleukin	Proleukin®
Altretamine	Hexalen®
Aminoglutethimide	Cytadren®
Anakinra	Kineret®
Anastrozole	Arimidex®
Asparaginase	Elspar®
Atazanavir sulfate	Reyatax®
Azathioprine	Imuran®
Azathioprine	Azasan
Basiliximab	Simulect®
Betamethasone	Celestone®
Bleomycin	Blenoxane®
Busulfan	Myleran®
Capecitabine	Xeloda®
Carboplatin	Paraplatin®
Carmustine	BiCNU® (BCNU)
Certolizumab pegol	Cimzia®
Chlorambucil	Leukeran®
Cidofovir	Vistide®
Cisplatin	Platinol®
Cladribine	Leustatin®
Cortisone	Cortone®
Cyclophosphamide	Cytoxan®
Cyclophosphamide	Neosar®
Cyclosporine	Gengraf®
Cyclosporine	Neoral®
Cyclosporine	Sandimmune®
Cytarabine	Cytarabine
Cytarabine	DepoCyt®
Dacarbazine	DTIC-Dome®

GENERIC NAME	TRADE NAME
Daclizumab	Zenopax®
Dactinomycin	Cosmegan®
Darunavir	Prezista®
Dasatinib	Sprycel®
Daunorubicin	Cerubidine®
Delavirdine	Rescriptor®
Denileukin diftitox	Ontak®
Dexamethasone	Dexamethasone
Didanosine	Videx®
Docetaxel	Taxotere®
Docetaxel	Docefrez®
Doxorubicin	Adriamycin®
Doxorubicin	Doxil®
Efavirenz	Sustiva®
Efavirenz/emtricitabine/tenofovir disoproxil Fumarate	Atripla®
Emtricitabine	Emtriva®
Emtricitabine/tenofovir disoproxil fumarate	Truvada®
Enfuvirtide	Fuzeion®
Epirubicin	Ellence®
Erlotinib	Tarceva®
Estramustine	Emcyt®
Etanercept	Enbrel®
Etoposide	Etopophos®
Etoposide	VePesid®
Etravirine	Intelence®
Everolimus	Afinitor®
Everolimus	Zortress®
Exemestane	Aromasin®
Floxuridine	Fluorodeoxyuridine®
Floxuridine	Ancobon®
Fludarabine	Oforta®
Fludarabine	Fludara®
Fosamprenavir calcium	Lexiva®
Gemcitabine	Gemzar
Golimumab injection	Simponi
Hydrocortisone	Cortef®

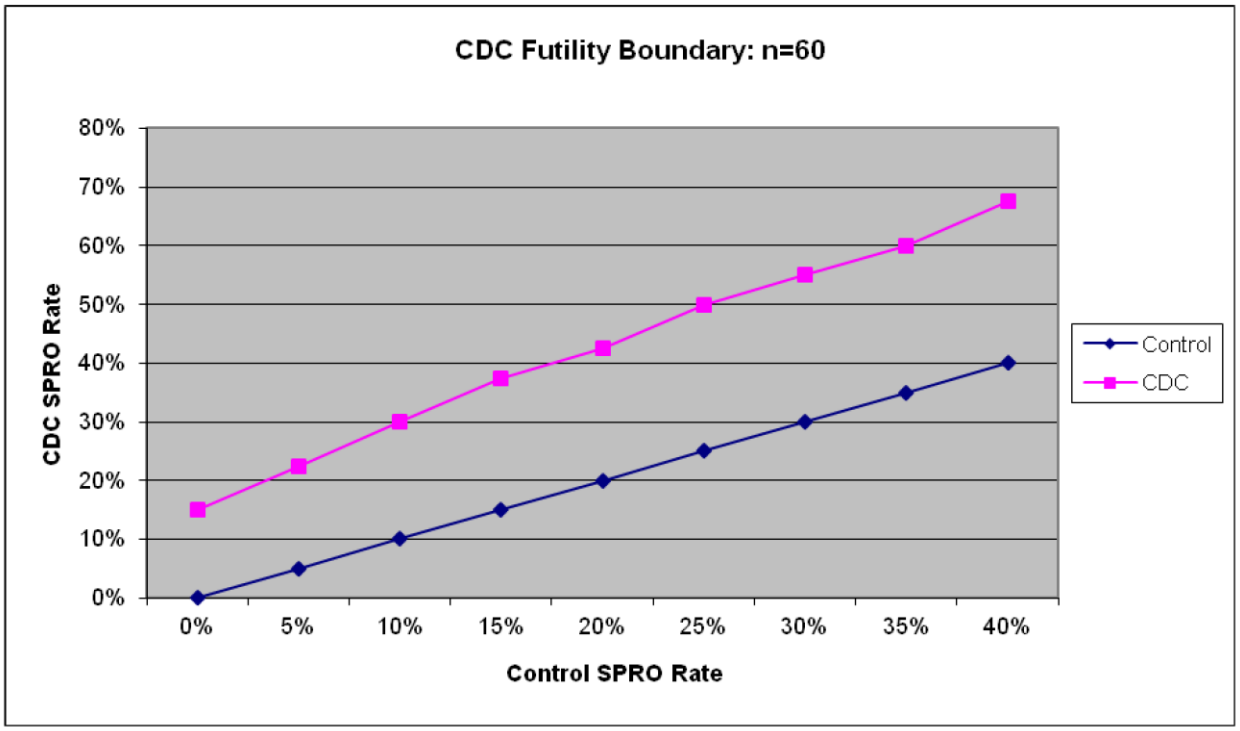
GENERIC NAME	TRADE NAME
Hydrocortisone	Hydrocortone®
Hydroxychloroquine	Plaquenil®
Hydroxyurea	Droxia®
Hydroxyurea	Hydrea®
Idarubicin	Idamycin®
Ifosphamide	Ifex®
Imatinib mesylate	Gleevac
Indinavir	Crixivan®
Infliximab	Remicade®
Interferon alfa-2a	Roferon-A®
Interferon alfa-2b	Intron-A®
Interferon alfacon-1)	Inferge ®
Interferon beta-1a	Avonex®
Interferon beta-1b	Betaseron®
Interferon beta-1b	Extavia®
Interferon beta-lb	Betaseron®
Interferon gamma-1b	Actimmune®
Interleukin-2	Proleukin
Irinotecan	Camptosar
Lamivudine	Epivir®
Lamivudine & Zidovudine	Combivir®
Lanreotide	Somatuline® Depot
Lapatinib	Tykerb®
Leflunomide	Arava®
Lenalidomide	Revlimid
Letrozole	Femara®
Leuprolide	Lupron®
Leuprolide	Eligard®
Lomustine	CeeNu® (CCNU)
Maraviroc	Selzentry
Mechlorethamine HCI	Mustargen®
Megestrol	Megace®
Melphalan	Alkeran®
Mercaptopurine	Purinethol®
Methotrexate	Rheumatrex®
Methotrexate	Trexall™
Methylprednisolone	Depo Medrol®

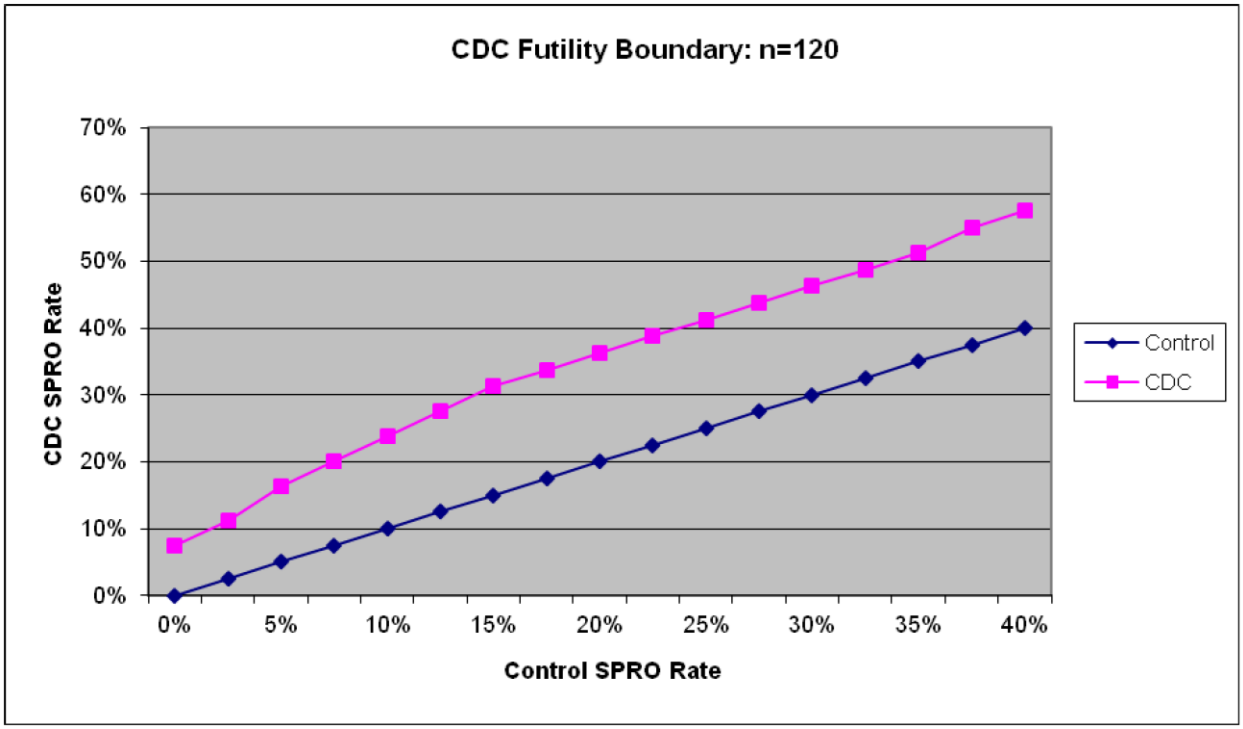
GENERIC NAME	TRADE NAME
Methylprednisolone	Solu-Medrol®
Methylprednisolone	A-Methapred
Methylprednisolone	Medrol®
Mitomycin	Mutamycin®
Mitotane	Lysodren®
Mitoxantrone	Novantrone®
Muromonab-CD3	Orthoclone-OKT3
Mycophenolate	CellCept®
Nelfinavir	Viracept®
Nevirapine	Viramune®
Nilotinib	Tasigna®
Octreotide acetate	Sandostatin®
Paclitaxel	Taxol®
Paclitaxel	Abraxane®
Pazopanib	Votrient®
Pegaspargase	Oncaspar®
Peginterferon alfa-2a	Pegasys®
Peginterferon alfa-2b	Peg-Intron®
Penicillamine	Cuprimine®
Prednisolone	Pediapred®
Prednisolone	Prelone®
Prednisone	Meticorten®
Procarbazine	Matulane®
Raltegravir	Isentress®
Ribavirin	Copegus®
Rilonacep	Arcalyst™
Ritonavir	Norvir®
Ritonavir/Lopinovir	Kaletra®
Rituximab	Rituxan®
Saquinavir	Invirase®
Sargramostim	Leukine®
Sirolimus	Rapamune®
Sorafenib	Nexavar®
Stavudine	Zerit®
Streptozocin	Zanosar®
Sulfasalazine	Azulfidine EN-tabs®
Sunitinib malate	Sutent®

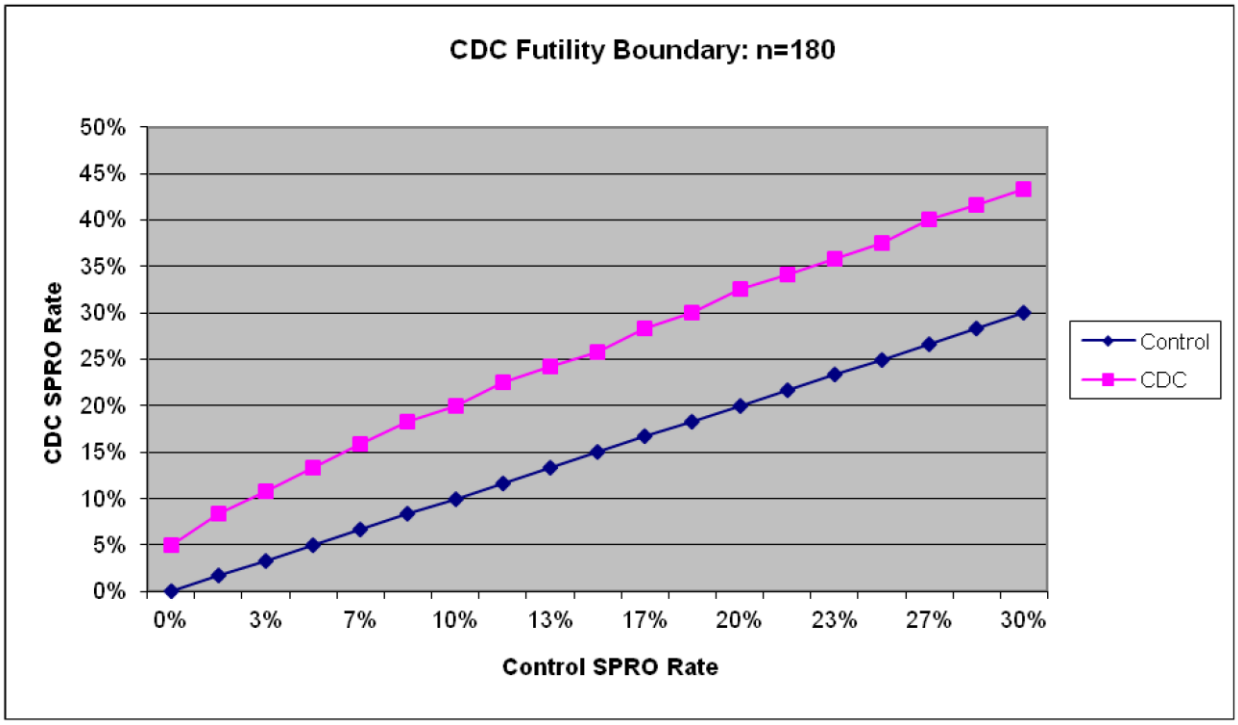
GENERIC NAME	TRADE NAME
Tacrolimus	Prograf®
Tamoxifen citrate	Nolvadex
Temozolomide	Temodar®
Temsirolimus injection	Torisel®
Teniposide	Vumon®
Tenofovir disoproxil fumarate	Viread®
Thalidomide	Thalomid®
Thioguanine	Tabloid®
Thiotepa	Thiotepa
Tipranavir	Aptivus®
Tocilizumab	Actemra®
Topotecan	Hycamtin®
Toremifene citrate	Fareston®
Trastuzumab	Herceptin®
Tretinoin	Vesanoid®
Tretinoin	Vesanoid®
Triamcinolone	Kenalog®
Triamcinolone	Aristospan®
Valrubicin	Valstar®
Vinblastine	Vinblastine
Vincristine	Vincristine
Vinorelbine	Navelbine®
Vorinostat	Zolinza®
Zalcitabine	Hivid®
Zidovudine	Retrovir®

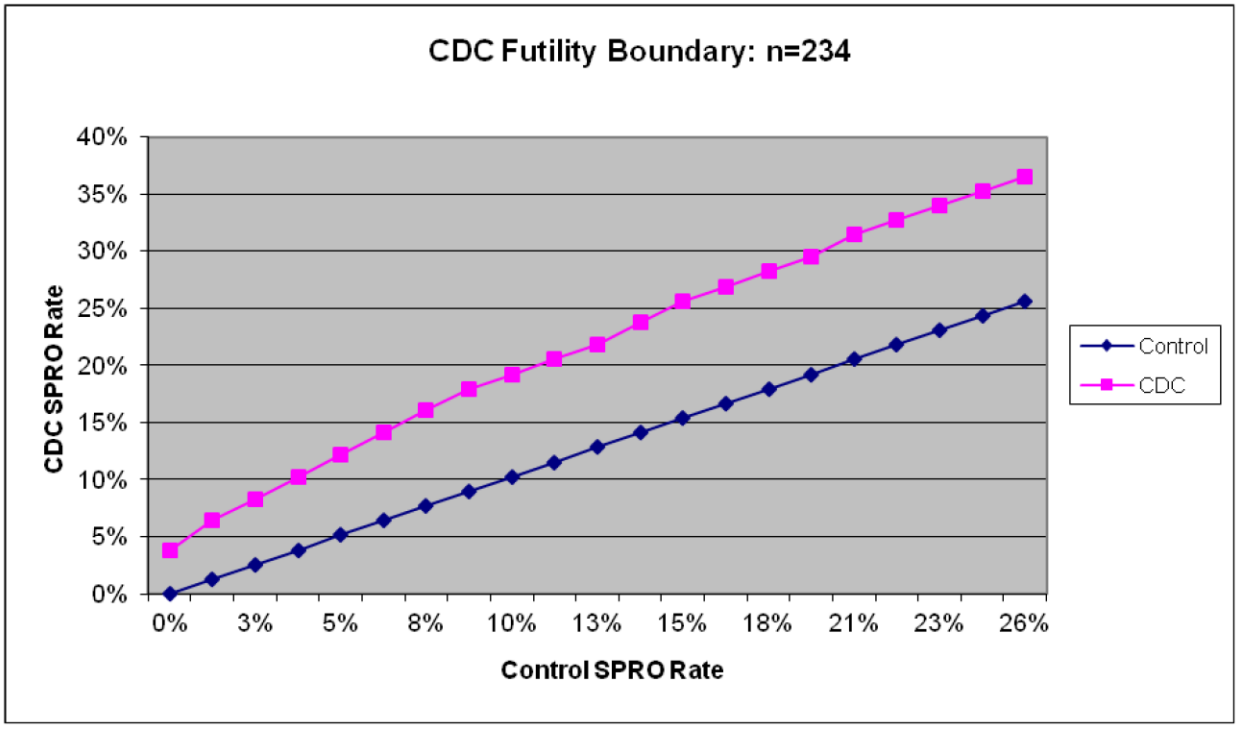
Appendix 3 CDC Futility Boundaries

The following four charts support DSMB safety monitoring of the Randomized Cohort. The excess for CDC-treated subjects will be of primary concern as data accrue. Charts have been prepared to correspond to accrual of 60, 120, 180, and 234 cases. The boundaries were computed using StatXact v7 (CyTel, Cambridge MA); a one-sided 95% exact test was performed assuming binomially distributed outcomes. The charts are illustrative and can be regenerated to correspond to the actual data accrued. The charts may be applied to any binary outcome pertaining to safety.




CDC Futility Boundary: n=120
CDC SPRO Rate
70%
60%
50%
40%
30%
20%
10%
0%
0%
5%
10%
15%
20%
25%
30%
35%
40%
Control SPRO Rate
Control
CDC


CDC Futility Boundary: n=180
CDC SPRO Rate
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0%
3%
7%
10%
13%
17%
20%
23%
27%
30%
Control SPRO Rate
Control
CDC


CDC Futility Boundary: n=234
CDC SPRO Rate
40%
35%
30%
25%
20%
15%
10%
5%
0%
0%
3%
5%
8%
10%
13%
15%
18%
21%
23%
26%
Control SPRO Rate
Control
CDC

Appendix 4 Sponsor Signature

Study Title:	Randomized, Double-Blind, Placebo-Controlled Phase I/II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with a Myocardial Infarction and Ischemic Left Ventricular Dysfunction (ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration, ALLSTAR)
Study Number:	1002-01
Original Protocol:	15 May 2012
Amendment 1:	13 June 2012
Amendment 2:	26 June 2012
Amendment 3:	30 January 2013
Amendment 4:	04 May 2013
Amendment 5:	25 October 2013
Amendment 6:	01 December 2014
Amendment 7:	15 May 2015
Amendment 7.1:	05 June 2015
Amendment 8:	15 January 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed: _____ Date: _____

[redacted]
Capricor, Inc.

Appendix 5 Investigator's Signature

Study Title:	Randomized, Double-Blind, Placebo-Controlled Phase I/II Study of the Safety and Efficacy of Intracoronary Delivery of Allogeneic Cardiosphere-Derived Cells in Patients with a Myocardial Infarction and Ischemic Left Ventricular Dysfunction (ALLogeneic Heart STem Cells to Achieve Myocardial Regeneration, ALLSTAR)
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Amendment 7:	15 May 2015
Amendment 7.1:	05 June 2015
Amendment 8:	15 January 2016

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____
<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>